

Diagnostic and experimental food challenges in patients with nonimmediate reactions to food

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Food challenge is a common and important part of the evaluation of patients with acute reactions to foods, such as milk, egg, wheat, or peanut. Furthermore, double-blind, placebo-controlled food challenges (DBPCFCs) have played a major role in the investigation of food allergy in children.¹ An important element of these challenges is that the responses are sufficiently rapid that increases in dose can be made every 30 minutes (or less). In adults the number of diagnostic challenges needed is much smaller. However, there are an increasing number of cases in adults in which the reactions to food are not rapid and in which the reactions only occur, or occur more consistently, if they are “enhanced.” The most common form of enhancement is exercise, but alcohol and aspirin can also play a role, either in diagnostic challenge or through naturally occurring exposure.² In this issue of the *Journal*, there is an important report on the effects of enhancement on oral food challenges (OFCs) with gluten in adult patients who presented with wheat-dependent exercise-induced anaphylaxis (WD-EIA).³

Several forms of allergy to wheat, its components, or its products continue to be reported (Fig 1).^{4,5} Although WD-EIA is well recognized, what is not well recognized is that these responses are dose dependent and that these patients are more likely to have reactions while exercising if they drank alcohol and ingested wheat prior to exercise. The current article confirms that these patients consistently have IgE antibodies to ω 5-gliadin (Table I).⁶ More importantly, they present evidence that reactions occur at a time when serum gliadin levels are increased.³

In 2014, 2 articles in the *Journal* reported the results of challenges in patients with delayed urticaria or anaphylaxis after eating red meat or pork kidney.^{7,8} Those patients all had serum IgE antibodies to galactose- α -1,3-galactose (alpha-gal).⁹ Those 2 reports share several features with the current report: (1) patients do not develop oral or other symptoms within the immediate timeframe after ingestion (30 minutes) that would facilitate identification of causative foods; (2) cofactor enhancement of OFCs with exercise, aspirin, alcohol, or combinations thereof might be necessary for elicitation of a positive challenge result^{3,8}; (3) analysis of IgE (skin or serum) to the component allergen or allergens responsible yields the highest sensitivity and specificity; and (4) the feasibility of carrying out in-clinic dose-response or placebo-controlled OFCs is low because of symptom delay or need for enhancement. Patients had to be admitted to an inpatient unit for 6 days to carry out the WD-EIA studies with control challenges.³ Unfortunately, it is difficult to arrange such admissions in the United States today.

The 2 recent reports on challenges in patients with IgE to alpha-gal have different features. In our study the salient feature was that the delay in response (ie, 3–5 hours) reported by the patients was confirmed in the OFC. In addition, the upregulation of CD63 on basophils *in vivo* occurred at the same time as the skin reactions.⁷ Nine of the 12 patients had visible urticaria, and 3 had significant increases in tryptase levels. What has not yet been established is which form of the antigen takes 3 hours or more to get into the circulation or, in particular, into the space surrounding mast cells in the skin. Dr Biederman's group in Germany identified 40 cases in which the striking feature was that most of the patients reported that pork kidney produced reactions more consistently and more rapidly than red meat.⁸ Despite these reactions occurring as early as 1 hour after ingestion, none of the patients studied reported immediate oral symptoms. Similar findings have been reported in 3 patients from France.¹⁰ Notably, upregulation of CD203c on basophils has been reported in patients with WD-EIA.¹¹

The current study on WD-EIA used exercise or alcohol and aspirin preceding exercise to enhance the challenges. In addition, doses of the gluten challenge were increased with bread made with gluten flour. It is important to recognize that the challenge protocol in the studies discussed here used higher doses for challenge than the initial doses used in testing children for immediate anaphylaxis to peanut, egg, or wheat.^{1,7,8,10} In the current report the authors found that some patients react after ingesting higher doses of gluten flour even without exercise, showing that ingestion of a sufficient amount of the specific component antigen might provoke a positive response without enhancement. Another significant feature of their results was the measurement of gliadin in the circulation after the challenge. Such measurements require further confirmation, but

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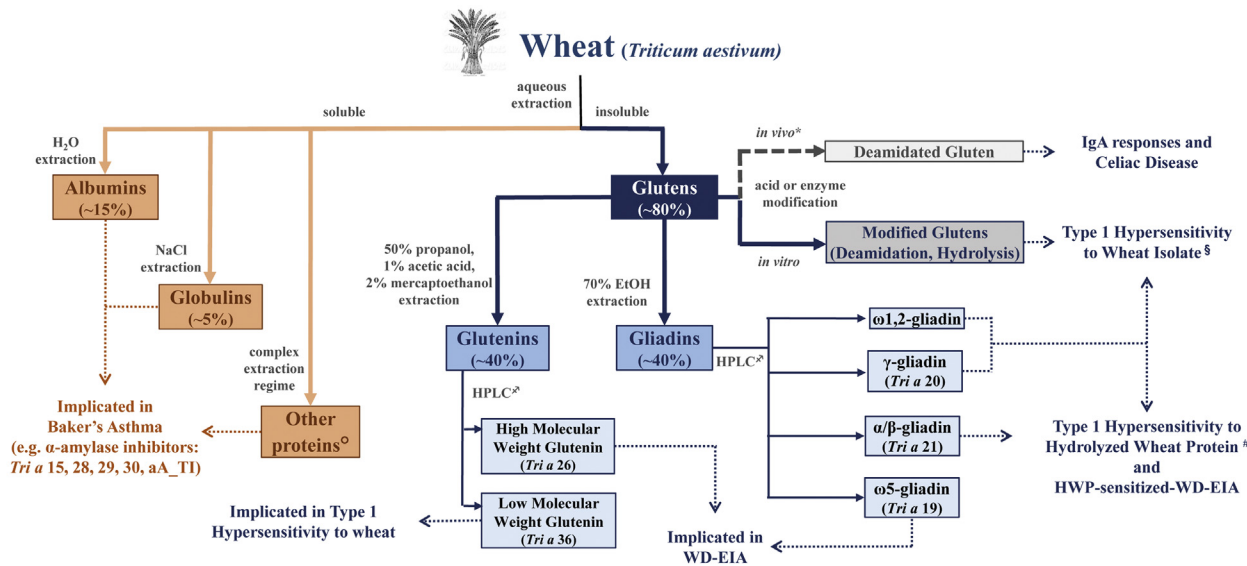
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° Includes α-amylase and protease inhibitors, glyceraldehyde-3-phosphate dehydrogenase (Tri a 34), serpin (Tri a 33), triosephosphate isomerase (Tri a 31), farinins, purinins, peroxidase, others

° HPLC: High Pressure Liquid Chromatography

* Via tissue transglutaminase

§ Used as food emulsifier and stabilizer. Found in: meat-based products; reconstituted meat; ready-cooked vegetable dishes; industry-processed soups, cakes, and cookies.⁵

HWP: Hydrolyzed Wheat Protein (wheat hydrolysate). Found in: Non-foods-- cosmetics, soaps, shampoo, and hair conditioner; Foods-- preserved foods, ham, and liver pâté.⁴

FIG 1. Wheat protein: Composition, Fractionation, and Modification in relation to reported forms of allergy.

TABLE I. Components of wheat available for *in vitro* IgE testing

Allergen or component allergen*	Source (taxonomic name) or IUIS nomenclature code	Allergen code†	Tested by ISAC‡	Availability for testing
Wheat	<i>Triticum aestivum</i>	f4	No	United States/Europe
Gluten	Tri a gluten	f79	No	United States/Europe
Gliadin	—	f98	No	Europe§
ω5-Gliadin	Tri a 19	f416	Yes	Europe§
Nonspecific LTP	Tri a 14	f433	Yes	Europe§
α-Amylase/trypsin inhibitor	Tri a aA_TI	—	Yes	—

IUIS, International Union of Immunological Societies; LTP, lipid transfer protein.

*There are 21 purified components of wheat identified on www.allergen.org, of which 9 are food allergens.

†Allergen Code designated by the Clinical and Laboratory Standards Institute.

‡Immuno Solid-phase Allergen Chip (ISAC) with 112 component allergens (experimental use in the United States and commercial use in Europe).

§Samples from the United States can be sent to the Phadia Immunology Reference Laboratory (PiRL) for these tests.

the evidence that cofactors can enhance absorption of wheat is interesting. Past attempts to measure levels of allergens, such as peanut, in the circulation after OFCs have not been successful (W. Burks, personal communication, 2012).

That some responses to food can be enhanced by cofactors such as exercise has been known for many years.¹² The major reasons for investigating cofactors in relation to WD-EIA were the inconsistency of reactions during exercise noted by patients and the inconsistency of reactions occurring with OFCs followed by exercise.³ Wheat is the best known allergen associated with food-dependent exercise-induced anaphylaxis; however, many other allergen-specific responses can be enhanced by exercise. In our experience exercise can also enhance urticarial or anaphylactic reactions associated with ingestion of celery, tomato, or mammalian meat; oral immunotherapy; trichophyton sensitization; and subcutaneous immunotherapy. In the last 2 years, we have heard an increasing number of patients report that their reactions to red meat occur more consistently or are more severe if they had also consumed alcohol. It appears that this cofactor can increase either the speed or the consistency of the reactions.

Sensitization to wheat is well recognized as a cause of immediate anaphylaxis but is also common in patients with eosinophilic esophagitis.^{1,13} Recent work from Japan has shown that application of hydrolyzed wheat proteins present in facial soap can result in cutaneous or rhinoconjunctival sensitization and present as WD-EIA.⁴ Studies in Europe have reported immediate hypersensitivity reactions to foods containing hydrolyzed wheat proteins or foods containing wheat isolate (deamidated gluten) in subjects who do not react after ingestion of foods containing native wheat proteins alone (Fig 1).^{5,14} Although routes of sensitization to wheat protein have been hypothesized to be oral/transintestinal or cutaneous, at present, it is not clear how the sensitization process differs between patients with WD-EIA, patients with immediate anaphylaxis to wheat, and those with eosinophilic esophagitis.

In conclusion, the report in this issue of the *Journal* provides important evidence that exercise-dependent reactions to wheat can be enhanced by alcohol and aspirin. In addition, they provide new evidence that the reactions relate to the absorption of gliadin. The clinical reactions to these challenges include objective changes in the skin and can be severe. It is important to realize that with such

delays in response, it is not feasible to carry out in-clinic challenges with progressive increases in dosage or in-clinic placebo-controlled challenges. Clearly, this form of challenge is capable of providing important information about the timing and quantity of absorption of the relevant allergen. Even if these studies are too difficult or time-consuming to become a procedure common to clinical practice, they should still be pursued to understand the mechanisms involved. Overall, it is clear that we have much to learn about the factors that can influence the timing and severity of nonimmediate reactions to food allergens in adults.

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