Original Article

Exercise Lowers Threshold and Increases Severity, but Wheat-Dependent, Exercise-Induced Anaphylaxis Can Be Elicited at Rest

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What is already known about this topic? Studies on how to establish the diagnosis of wheat-dependent, exercise-induced anaphylaxis (WDEIA) are sparse and a controlled challenge protocol only rarely applied.

What does this article add to our knowledge? This large study demonstrates that exercise is not an essential trigger because WDEIA can be verified in a challenge setting at rest (without cofactors) if the culprit food (gluten) is ingested in sufficiently high amounts.

How does this study impact current management guidelines? The proposed challenge algorithm with gluten ± treadmill exercise is a safe confirmatory test and demonstrates that exercise in WDEIA is an augmentation factor able to lower threshold and increase severity.

BACKGROUND: Wheat-dependent, exercise-induced anaphylaxis (WDEIA) is a severe form of allergy in which exercise is being considered as mandatory. The diagnosis is often complex and the clinical reproducibility low.
OBJECTIVE: The aims of this study were to establish a standardized challenge method for the diagnosis of WDEIA and to investigate whether exercise is an essential trigger factor or alternatively an augmentation factor able to lower threshold and increase severity.
METHODS: We investigated 71 patients (age, 18.6-73.7 years) with a case history of WDEIA. Skin prick test (SPT) and measurement of specific IgE (sIgE) were followed by an oral food challenge with gluten at rest and in combination with treadmill exercise.
RESULTS: A clinical reaction was elicited in 47 of 71 (66%), and in 26 of these (37%) the reaction could be elicited at rest. The median dose required at rest was 48 g (8-80 g) and in combination with exercise 24 g (4-80 g). Severity was significantly higher with exercise (2.3) than at rest (1.1) using Sampson severity score. In the challenge, SPT was positive to wheat in 93.6% (44 of 47) and to gluten in 95.7% (45 of 47). sIgE to wheat, gliadin, and omega-5 gliadin was present in 78.7% (37 of 47), 76.5% (36 of 47), and 91.4% (43 of 47) of the patients. Receiver operating characteristic—curve analysis for sIgE to omega-5 gliadin, a component of the gluten fraction and the major allergen in WDEIA, showed best sensitivity (91%) and specificity (92%) when gluten was combined with exercise.
CONCLUSIONS: A challenge test with gluten at rest and combined exercise is a safe confirmatory test for WDEIA. A reaction can be elicited at rest (without exercise), but exercise is able to lower the threshold and increase the severity. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:514-20)

Key words: *Anaphylaxis; Wheat-dependent, exercise-induced anaphylaxis; Gluten; oral challenge; Exercise challenge; Specific IgE; Skin prick test*

INTRODUCTION

Wheat-dependent, exercise-induced anaphylaxis (WDEIA) is a rare, but severe and potentially life-threatening disorder characterized by anaphylactic reactions after wheat ingestion in combination with physical exercise.[1] Exercise is often denoted as an obligatory cofactor for eliciting WDEIA, although the role and pathophysiological mechanisms remain unclear.

Other cofactors such as infection, aspirin/nonsteroidal anti-inflammatory drug, alcohol, and stress in case reports or in small series have been reported to be equally effective when substituted or combined with exercise in eliciting symptoms together with an offending food.[2-8]

Wheat proteins are classified into water/salt-soluble (albumin and globulin) and water/salt-insoluble (prolamin/gluten) fractions. The latter group comprises glutenin (high molecular weight glutenin and low molecular weight glutenin) and gliadin

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Abbreviations used
sIgE- Specific IgE
SPT- Skin prick test
WDEIA- Wheat-dependent, exercise-induced anaphylaxis

(α-, β-, γ, and ω-gliadin), where especially recombinant omega-5 gliadin has been described as the major allergen in WDEIA.[9,10]

The diagnosis of WDEIA is challenging, because even in typical case histories a reaction cannot always be reproduced during challenge with wheat in combination with exercise.[11,12] Recently, Brockow et al[13] have shown that challenge with high-dose purified gluten and supplemental cofactors increased the diagnostic sensitivity in patients with positive specific IgE (sIgE) to omega-5 gliadin.

The aims of this study were to establish a new standardized challenge method for the diagnosis of WDEIA and to investigate whether exercise is either an essential trigger factor or an augmentation factor able to lower threshold and increase severity.

METHODS

Seventy-one patients (36 women and 35 men) aged 18.6 to 73.7 years (mean age, 42.9 years) with a case history of WDEIA attended the Odense Research Center for Anaphylaxis, at Odense University Hospital, Denmark, between April 2014 and November 2016. At the first study visit, medical history, skin tests, blood sampling, and clinical examination were performed. Patients' characteristics are presented in Table I. Analysis for tryptase and KIT D816V mutation[14] in peripheral blood was performed in 67 patients, all negative. No patients had any history of wheat allergy in childhood, and serologic testing (n = 71) for celiac disease using the tTG-IgA test (in-house ELISA, Odense University Hospital, Odense, Denmark) was all negative. At the next visit, all 71 patients were challenged with gluten (see later) at rest (without cofactors) and on a separate day with gluten combined with exercise. Twenty-three patients had previously been challenged with wheat bread (44 g wheat flour) combined with exercise on a treadmill.[11] Gluten was used rather than wheat because this fraction contains an increased concentration of the allergens that may be responsible for WDEIA.

The study was approved by the Regional Committees on Health Research Ethics for Southern Denmark (Project ID 20140012) and the Danish Data Protection Agency (no. 14/4999). Informed consent was obtained from all patients.

Specific IgE and skin prick test

Measurements of serum levels of sIgE to wheat (f4), gliadin (f98), and recombinant omega-5 gliadin (f416) were analyzed before challenge using the ImmunoCAP system (Thermo Fisher Scientific, Uppsala, Sweden). Positive results were defined as 0.10 kU/L or more. Skin prick test (SPT) was performed on the volar surface of the forearm according to European Academy of Allergy and Clinical Immunology (EAACI) guidelines[14] with wheat (100 mg/mL) and gluten (10 mg/mL) extracts in glycerol solvent (RefLab Aps, Copenhagen, Denmark) and prick-to-prick test with native wheat flour and purified, food-grade gluten (Jean Pütz Products, Cologne, Germany). A positive SPT result was defined as a mean wheal diameter of 3 mm or more. Histamine dihydrochloride (10 mg/mL, ALK, Copenhagen, Denmark) and physiological saline were used as positive and negative controls. Antihistamines and other drugs interfering with SPT were discontinued at least 3 days before testing.

Challenge protocol

The challenge protocol was based on an initial challenge with gluten at rest (without cofactors) followed, on a separate day, by a challenge with gluten in combination with treadmill exercise. Increasing amounts of baked bread (80 g formed as rolls and baked at 200°C for 10 minutes) of purified gluten flour (Jean Pütz Products, Cologne, Germany) were administered orally at 60-minute intervals to a cumulated dose of 80 g (8 g - 16 g - 24 g - 32 g) or until objective signs occured. Based on the threshold at rest, the first amount of gluten in combination with exercise was 1/10 of the cumulated threshold and hereafter 2/10, 3/10, and 4/10 of the cumulated threshold at rest were given every 60 minutes or until an objective reaction occurred.

The exercise challenge protocol was modified from the protocol for the diagnosis of ischemic heart disease by Bruce et al.[15] The challenge was performed on a treadmill (Technogym Excite+ Run Now 900) starting with 4 aerobic phases of 15 minutes adapted to each patient's physical abilities, with each aerobic phase starting 30 minutes after ingestion of gluten. Finally, on the basis of the aerobic workload, a multistage exercise test was performed, where both pace and inclination were increased every minute to reach physical fatigue in the patient. Each multistage intensity series was followed by 1 minute of light workload (5 km/h and no inclination). Serum tryptase level was measured 60 to 120 minutes after a positive challenge (see Figure 1) and severity according to Sampson[16] was recorded. Only objective signs were included for the determination of threshold. Serum lactate level was measured (Radiometer ABL-90-FLEX, Radiometer, Copenhagen, Denmark) before each challenge (± exercise) and at time of reaction or in case of no reaction after the multistage exercise challenge at physical fatigue.

A negative challenge at rest was defined as absence of objective signs within 2 hours of administration of the last dose (cumulated 80 g). A negative challenge during exercise was defined as absence of objective signs within 2 hours of administration of the cumulated threshold dose and exercise. Patients were continuously monitored by an MD and a registered nurse during challenge, with emergency equipment at hand. The time interval between challenges with gluten with or without exercise had a median of 61 days.

Statistical analysis

For the purpose of statistical analysis, sIgE values of less than 0.10 kU/L were assigned a value of 0.01 kU/L. Results for thresholds are given as medians and 25-75 percentiles. Statistical significance was calculated using the Wilcoxon signed-rank test, whereas results for severity are given as means and statistical differences calculated using Student *t* test. Statistical significance was defined at a *P* value of less than .05. Sensitivity and specificity of sIgE to wheat (f4), gliadin (f79), and omega-5 gliadin (f416) were examined by receiver operator characteristic curves. Statistical analyses were performed using statistical software (STATA version 14.0, StataCorp, College Station, Texas).

RESULTS

Challenge results

The flow chart of all challenges for the 71 patients with a case history of WDEIA is presented in Figure 2. All patients completed an oral challenge with increasing amounts of gluten at rest, whereof 68 patients (96%) completed the challenge with gluten in combination with exercise (see Figure 2).

Figure 3 shows the paired thresholds with and without exercise (see Figure 3, *A*), and the corresponding severity of the

TABLE I. Patient characteristics, case history, and test results

	Characteristic	Challenge positive (± exercise)	Challenge negative (± exercise)
Characteristics and case history	Sex	23 females (51%), 24 males (49%)	13 females (54%), 11 males (46%)
	Age (y)	Mean, 43.0 ± 12.9 (range, 20.2-73.3)	Mean, 40.8 ± 14.4 (range, 18.6-64.8)
	History of atopy	Allergic rhinitis (n = 7), atopic dermatitis (n = 1), asthma (n = 1)	Allergic rhinitis (n = 8), atopic dermatitis (n = 4), asthma (n = 2)
	No. of reactions	Mean, 16 ± 23 (median, 7; range, 1-100)	Mean, 4 ± 4 (median, 3; range, 1-16)
	Duration of disease (y)	Mean, 8.0 ± 8.0 (range, 0.1-39.2)	Mean, 4.2 ± 4.1 (range, 0.1-14.8)
	Symptoms in case history	Urticaria (n = 47), pruritus (n = 35), hypotension (n = 30), unconsciousness (n = 24), respiratory (n = 19), tachycardia (n = 23), angioedema (n = 17), flushing (n = 16), nausea/vomiting (n = 5), abdominal pain (n = 2), rhinitis (n = 1), conjunctivitis (n = 1), diarrhea (n = 0)	Urticaria (n = 15), pruritus (n = 19), hypotension (n = 8), unconsciousness (n = 4), respiratory (n = 6), tachycardia (n = 3), angioedema (n = 8), flushing (n = 7), nausea/vomiting (n = 4), abdominal pain (n = 3), rhinitis (n = 0), conjunctivitis (n = 0), diarrhea (n = 4)
	Possible other triggers	Aspirin/NSAID (n = 9), stress (n = 7), alcohol (n = 4), infection (n = 4), menstruation (n = 1), none (n = 0)	Aspirin/NSAID (n = 4), alcohol (n = 3), stress (n = 2), none (n = 6)
	Reaction related to exercise	Before (n = 0), during (n = 34), after (n = 28)	Before (n = 0), during (n = 12), after (n = 13)
	Intensity of exercise	Mild (n = 19), moderate (n = 15), intense (n = 39)	Mild (n = 5), moderate (n = 5), intense (n = 18)
	Wheat ingestion related to exercise	Before (n = 47), during (n = 0), after (n = 4)	Before (n = 24), during (n = 0), after (n = 0)
	Time from ingestion to reaction (min)	Mean, 71 ± 52 (median, 60; range, 10-240)	Mean, 119 ± 52 (median, 120; range, 30-240)
	Reaction to cereals	Wheat (n = 47), rye (n = 4), barley (n = 1), oat (n = 0)	Wheat (n = 14), rye (n = 1), unknown (n = 9)
Test results	sIgE wheat	Positive 37 of 47 (median, 1.12 kU/L; range, 0-18.7 kU/L)	Positive 3 of 24 (median, <0.10 kU/L; range, 0-3.8 kU/L)
	sIgE gliadin	Positive 36 of 47 (median, 1.38 kU/L; range, 0-11.5 kU/L)	Positive 2 of 24 (median, <0.10 kU/L; range, 0-0.6 kU/L)
	sIgE omega-5 gliadin	Positive 43 of 47 (median, 7.20 kU/L; range, 0-46.7.0 kU/L)	Positive 2 of 24 (median, <0.10 kU/L; range, 0-2.98 kU/L)
	SPT wheat	Positive 44 of 47 (median, 5.5 mm; range 0-10.0 mm)	Positive 10 of 24 (median, 0 mm; range, 0-7.0 mm)
	SPT gliadin	Positive 40 of 47 (median, 5.0 mm; range, 0-10.5 mm)	Positive 6 of 24 (median, 0 mm; range, 0-6.5 mm)
	SPT gluten	Positive 45 of 47 (median, 5.0 mm; range, 0-11.5 mm)	Positive 8 of 24 (median, 0 mm; range, 0-7.0 mm)

NSAID, Nonsteroidal anti-inflammatory drug.

reaction (see Figure 3, *B*). At rest, 26 (37%) patients experienced an objective clinical reaction with a median threshold of 48 g (range, 8-80 g), and they all had a reaction to the gluten + exercise challenge, except for 3 patients, who were excluded for various reasons (see legend to Figure 2). In 21 of 45 (48%) patients, no reaction to the maximum cumulated dose of 80 g of gluten at rest was obtained, but was subsequently elicited by addition of exercise, while 24 patients were challenge negative also in combination with exercise, even at anaerobic conditions.

The median dose of gluten required to elicit a reaction in combination with exercise (n = 44) was 24 g (range, 4-80 g). Median time to reaction after intake of the eliciting dose at rest was 45 minutes (25-70 min) with a median total challenge time of 150 minutes (25-240 min). When gluten was combined with exercise, the median time to reaction was 5 minutes after finalizing the eliciting exercise cycles (−5 min to −25 min), with a median total challenge time of 120 minutes (37-240 min) and median number of 2 exercise cycles performed on the treadmill.[1-4]

In the 23 patients with a positive challenge both at rest and in combination with exercise, a mean decrease of 62% in threshold was observed (median, 25 g; range, 0-72 g) ($P < .05$). Mean severity score at rest was 1.1, whereas it was significantly higher in combination with exercise (2.3) ($P < .05$). Severity remained unchanged in 16 patients, but their reaction was elicited at a lower threshold when combined with exercise (median difference, 26.8 g; range, 0-72 g), except for 1 patient in whom threshold (32 g) and severity score of 2 remained unchanged (see Figure 3, *A* and *B*, marked with ●).

A significant elevation in serum tryptase level was found after 6 positive challenges (rest = 2, exercise = 4) (median, 11.7 μg/L; range, 7.3-60.5 μg/L)[17] whereof 2 patients experienced a severity

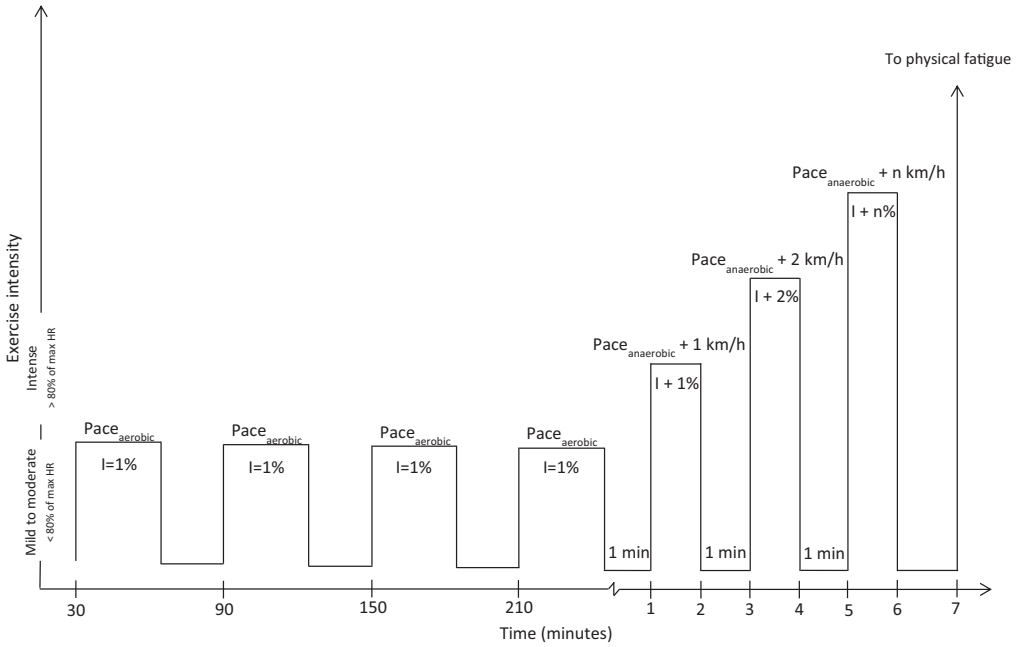


FIGURE 1. Challenge procedure for gluten in combination with exercise. *HR*, Heart rate; *I*, inclination in percent; $Pace_{aerobic}$, individual start pace (8-12 km/h) for 15 minutes; $Pace_{anaerobic}$, $Pace_{aerobic}$ sequentially increased by + 1 km/h to become anaerobic.

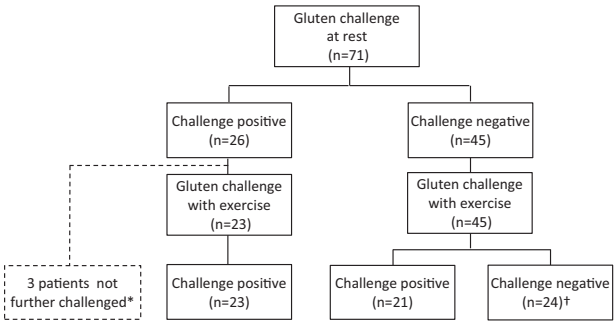


FIGURE 2. Flow chart of patients and challenge results. *Three patients were not challenged with gluten combined with exercise: pregnancy (n = 1), severe anaphylaxis (grade 5) (n = 1), and refused (n = 1). †Of the 24 patients, 3 were subsequently diagnosed with allergy to celery, to hydrolyzed wheat protein (3), to wheat in combination with aspirin (2), to buckwheat (1), and to shrimp (1). A total of 14 patients were lost to follow-up.

score of 5, 1 patient a severity score of 4, and 3 patients a severity score of 2, respectively. Symptoms and signs during challenge with purified gluten required treatment according to EAACI guidelines[18] in 19 patients: oral nonsedating antihistamine (5 mg of levocetirizin) (n = 16), β_2-inhalation (5 mg/mL salbutamol) (n = 4), methylprednisolone (80 mg) (n = 3), and epinephrine (n = 2).

Twenty-four patients (13 women and 11 men) aged 18.6 to 64.8 years (mean age, 40.8 ± 14.4 years) were challenge negative both with gluten at rest and in combination with exercise. Their case history revealed significantly fewer reactions and less convincing timing of the reactions, with median time to reaction of 2 hours after food ingestion ($P < .05$) (Table I). In 9 of 24 cases, challenges were performed for exclusion of wheat allergy because wheat was part of the meal eliciting their initial reaction.

Serum lactate measurements before challenge showed mean levels of 1.2 mmol/L (range, 0.4-2.2 mmol/L), at reaction 1.5 mmol/L (range, 0.5-7.5 mmol/L), and at a negative challenge 2.9 mmol/L (0.8-8.2 mmol/L). All reactions were elicited without a significant increase in serum lactate level.

Only 2 of the 24 negative patients had positive IgE to omega-5 gliadin (1.05 kU/L and 2.98 kU/L) and were later diagnosed with WDEIA confirmed by the addition of aspirin (data not shown), although a reaction could neither be elicited at rest nor with gluten in combination with exercise only. Preliminary data suggest aspirin and alcohol to be cofactors able to lower threshold as well as exercise and will be further investigated.

The diagnostic values of sIgE and SPT

In the challenge-positive patients (n = 47), SPT responses to raw wheat were positive in 93.6% (44 of 47), to gliadin in 85.1% (40 of 47), and to gluten in 95.7% (45 of 47), with no significant difference in wheal diameter between wheat (5.5 ± 2.0 mm; range, 0-10.0 mm), gliadin (5.0 ± 2.7 mm; range, 0-10.5 mm), and gluten (5.0 ± 2.3 mm; range, 0-11.5 mm). sIgE to wheat, gliadin, and omega-5 gliadin were present in 78.7% (37 of 47), 76.5% (36 of 47), and 91.4% (43 of 47), respectively, of the challenge-positive patients, with a median of 1.12, 1.38, and 7.30 kU/L, respectively.

In the 24 challenge-negative patients, SPT responses to wheat were found in 41.6% (10 of 24) and to gluten in 33.3% (8 of 24) and sIgE levels were elevated to wheat in 16.7% (3 of 24), to gliadin in 8.3% (2 of 24), and to omega-5 gliadin in 8.3% (2 of 24). sIgE levels to omega-5 gliadin were significantly higher compared with the sIgE levels to wheat and gliadin ($P < .0001$) in the challenge-positive, but not in challenge-negative patients.

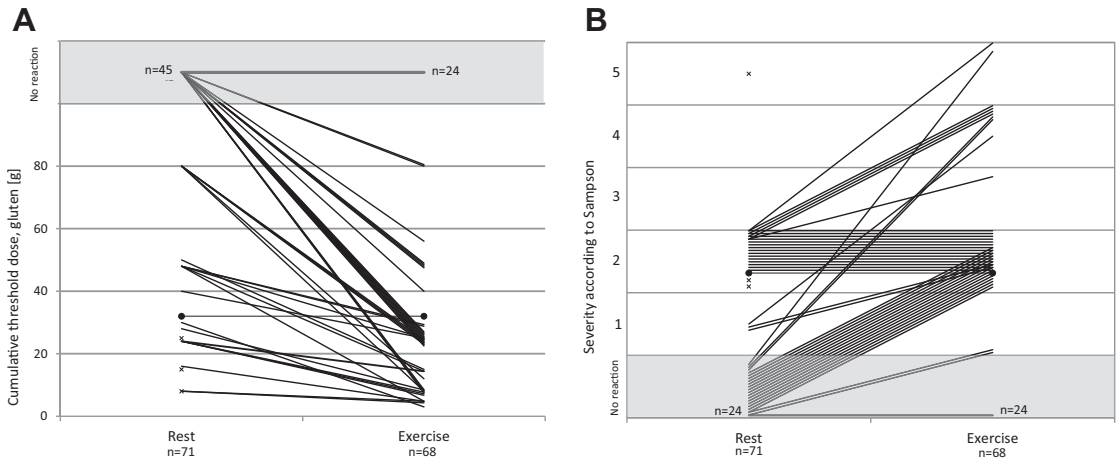


FIGURE 3. **A**, Comparative gluten thresholds at rest and with exercise for challenged patients. **B**, Severity according to Sampson at rest and with exercise.

According to the receiver operating characteristic—curve analysis (see Figure 4), the cutoff value for sIgE to omega-5 gliadin producing the best sensitivity (91%) and specificity (92%) was 0.74 kU/L when oral challenge with gluten was combined with exercise.

DISCUSSION

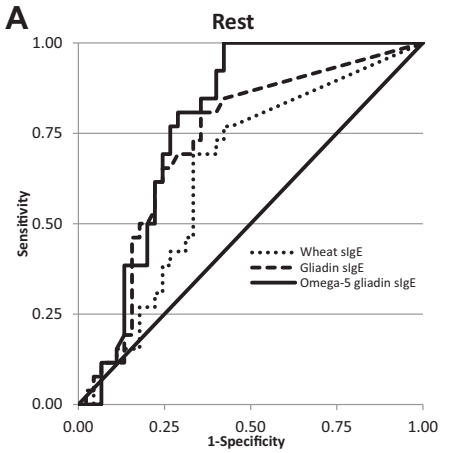
The diagnosis of WDEIA has until now been characterized by a low clinical reproducibility, which, even in cases with an evident case history and positive sIgE to omega-5 gliadin,[11,12] often results in a prolonged diagnostic delay. Many patients have experienced numerous allergic reactions, including anaphylaxis, before the correct diagnosis is established, and WDEIA/food-dependent, exercise-induced anaphylaxis (FDEIA) may be mistaken for other diseases such as acute or chronic urticaria, cholinergic urticaria, exercise-induced anaphylaxis, idiopathic anaphylaxis, other food or drug allergies, or even nonallergic diseases.[1] An improved diagnostic algorithm with a high predictive value is therefore needed.

There are 3 important and unique findings in this study: First, a reaction can be elicited without exercise in more than half the patients with WDEIA if they are challenged with a sufficiently high amount of purified gluten. Second, exercise in conjunction with wheat intake lowers the threshold and/or increases the severity of the reaction, and should therefore be considered as an augmentation factor. Third, the method presented here with purified gluten as allergen source and with/without exercise is a reliable and sensitive challenge test for diagnosing WDEIA, without compromising patient safety.

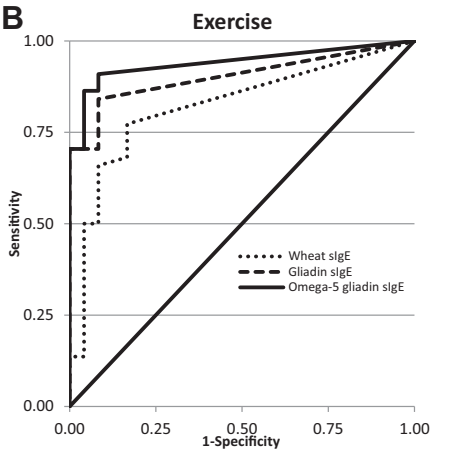
Gluten is the non—water-soluble and main strutural protein of wheat and contains the ethanol-soluble gliadins and acid/base-soluble glutenins. Common wheat bread contains approximately 8% to 12% (w/w) gluten, and thus the maximal cumulated dose given (80 g) is equlivalent to approximately 800 g of regular wheat flour or 55 slices of common toastbread. In our study, WDEIA could be elicited in 55% (26 of 47) of patients in the absence of exercise. Thus, a discrepancy is present between the eliciting amount reported in the patient case histories and the clinical thresholds obtained by challenge. Our findings indicate that WDEIA is a regular (non—exercise-dependent) wheat allergy where thresholds are very high in a daily life setting. Theoretically, if gluten doses were further increased at rest all patients could potentially have a reaction at some point. Exercise or other cofactors such as aspirin/nonsteroidal anti-inflammatory drugs or alcohol are required to lower the threshold sufficiently to elicit reactions with intake of physiological amounts of gluten.[19] Metabolism at rest is not equal to 0 but is, however, markedly increased during exercise. Therefore, the crucial variable parameters involved for a reaction may be the amount of gluten and calories burned.

Before the article by Brockow et al[13] it was believed that WDEIA was dependent on exercise or at least another cofactor (eg, aspirin, alcohol, or infection).[3,4,6-8,19] With this study we systematically and on a larger scale confirm previous findings, that WDEIA can be elicited without a cofactor present. Furthermore, this study demonstrates that exercise lowers the threshold dose and even increases the severity of reactions at a lower threshold level compared with resting conditions. Whether a challenge, and hereby a risk of a potential (severe) allergic reaction, is a stressful circumstance and that stress can act as a cofactor may be likely but also individual for each patient and perhaps dependent on the number of previous challenges.

Exercise is the best-known and most frequently reported cofactor.[20] All patients reported exercise as a cofactor (see Table I), ranging from strenuous physical exercise such as jogging to milder exercise, for example, brisk walking or house/garden work. Like the wide range in threshold found at rest (8-80 g), the intensity of treadmill exercise was individualized and adapted to physical abilities. All reactions were elicited during regular exercise cycles with no significant elevation in serum lactate levels and before the multistage exercise challenge. It is noteworthy that all patients except 1 (who had a reaction during exercise, 5 minutes before the termination of the running cycle) had a reaction after cessation of running and further at aerobic conditions. No correlation between exercise intensity, severity, or threshold was found. As reported in their history, patients most often had a reaction during or just after finishing exercise, which correlated well with our challenge results, where most patients developed a reaction immediately after exercise.



sIgE	No.	AUC	Cut-off-value kU/L	Sensitivity (%)	Specificity (%)
Wheat	71	0.644	0.67	69	67
Gliadin	71	0.725	1.26	65	76
Omega-5 gliadin	71	0.782	2.89	81	71



sIgE	No.	AUC	Cut-off-value kU/L	Sensitivity (%)	Specificity (%)
Wheat	68	0.821	0.38	77	83
Gliadin	68	0.903	0.13	84	92
Omega-5 gliadin	68	0.940	0.74	91	92

FIGURE 4. Receiver operating characteristic curves of sIgE to wheat (f4), gliadin (f98), and omega-5 gliadin (f416) at rest (**A**) and in combination with exercise (**B**). *AUC*, Area under the curve.

Different mechanisms by which exercise acts as a cofactor have been hypothesized,[21] but data are sparse so further investigations into the precise pathomechanism of WDEIA are needed.

Up to now no reliable, standardized, and safe diagnostic challenge method for WDEIA has been published: in our previous experience, only 21% of suspected cases of WDEIA were confirmed by challenge with common wheat in combination with exercise challenge and other cofactors.[11] This is in agreement with previously published WDEIA case series, where the diagnosis often is based on sIgE to omega-5-gliadin or challenge with common wheat in combination with different cofactors (eg, exercise, aspirin, and alcohol).[2,4-8,13] A precise diagnosis of WDEIA is important, because undiagnosed WDEIA leads to a high risk of anaphylaxis, because wheat is a very common source of food, and because FDEIA in the worst case can be fatal.[22,23] By using gluten together with exercise we were able to confirm the diagnosis in 95.9% of patients, whereof the most frequent symptom was urticaria (Sampson severity score 2); epinephrine was used in only 2.1% (n = 2) of the challenges.

Omega-5 gliadin is strongly associated with WDEIA[9,10] as shown by Brockow et al[13] where gluten used in combination with different cofactors resulted in a positive challenge rate of 100% in patients with positive sIgE to omega-5 gliadin. Although we found 91.8% having positive omega-5 gliadin among the challenge positive, 8.2% (n = 4) had a negative (<0.35 kU/L) sIgE to omega-5 gliadin. To exclude exercise-induced anaphylaxis, the 4 patients underwent a fasting exercise challenge also with negative outcome. Our results indicate, as previously shown,[10,13] that a positive omega-5 gliadin strongly correlates with WDEIA, whereas no correlation between sIgE to omega-5 gliadin level and threshold and severity was established.

The criterion standard for the diagnosis of food allergy is a food challenge,[14] but our results demonstrate that oral food challenge with exercise should be considered the criterion standard for diagnosing WDEIA.

There are limitations to this study. First, it is a single-center study with oral food challenge. Second, the amounts of gluten necessary for eliciting a reaction at rest are unphysiologically high, although approaching real-life conditions during exercise. However, the primary objective of this study was not to find individual thresholds but to establish a reliable challenge method and also evaluate exercise as a cofactor. A confirmatory test for the diagnosis of WDEIA is also helpful for providing guidelines for the individual patient, that is, whether the patient should be advised strictly to avoid gluten (wheat, rye, and barley)[9] or recommend avoidance only in combination with exercise (exercise abstinence 4 hours before and after gluten ingestion). A clinical conclusion may be that challenge tests with high doses of gluten are able to elicit a clinical reaction to wheat products, and the fact that a reaction does not take place after every intake of wheat can thus be explained by intake of different amounts of wheat combined with different levels of exercise at different occasions. Therefore, when taking a clinical history, the practitioner should try to assess the volume of wheat ingestion before each reaction. In conclusion, a challenge test with gluten at rest followed by a combined exercise and gluten challenge seems to be a suitable and safe confirmatory test for WDEIA, independent of the level of sIgE to omega-5 gliadin.

Historically, the term WDEIA has been used to describe anaphylactic reactions after a combination of wheat ingestion and physical exercise but we demonstrated that WDEIA can be elicited without exercise if the challenge dose is sufficiently high; therefore, exercise might merely be an augmentation factor able to lower the threshold and increase the severity.

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