

The Sensitivity and Clinical Course of Patients with Wheat-Dependent Exercise-Induced Anaphylaxis Sensitized to Hydrolyzed Wheat Protein in Facial Soap - Secondary Publication

Makiko Hiragun¹, Kaori Ishii¹, Takaaki Hiragun¹, Hajime Shindo¹, Shoji Mihara¹, Hiroaki Matsuo² and Michihiro Hide¹

ABSTRACT

Background: Recently, an increasing number of patients with wheat-dependent exercise-induced anaphylaxis (WDEIA) have been reported in Japan. Most of them had developed this condition during or after using hydrolyzed wheat protein (HWP)-containing soap (HWP-WDEIA).

Methods: To clarify the relation between WDEIA and HWP-containing soap and their prognosis, we retrospectively studied the patients who visited Hiroshima University Hospital and were diagnosed as WDEIA from January 2010 to June 2011. We took detailed clinical histories, performed skin prick tests, serum immunoassays for antigen-specific IgE and basophil histamine release test, and followed up their clinical courses after the diagnosis.

Results: Among 36 patients with WDEIA, 30 patients had used only one type of HWP-soap. The patients with HWP-WDEIA were mainly women and had developed facial symptoms and angioedema. They suffered from blood pressure reductions less frequently than patients with conventional WDEIA. The levels of gluten-specific IgE were higher than those of omega-5 gliadin in patients with HWP-WDEIA ($P < 0.05$, One-way ANOVA). All patients with HWP-WDEIA were positive against HWP in histamine release test. Among the conventional wheat antigens, glutenins induced the highest histamine release from basophils of patients with HWP-WDEIA. The sensitivities of patients against glutes and glutenins were reduced over months along with the discontinuance of HWP-soap.

Conclusions: The development of HWP-WDEIA is associated with the use of HWP-soap. The sensitivity to HWP that cross reacts with non-processed wheat may be reduced or possibly cured after the discontinuation of HWP-soap.

KEY WORDS

clinical course, histamine release test, hydrolyzed wheat protein (HWP), IgE, wheat-dependent exercise-induced anaphylaxis (WDEIA)

¹Department of Dermatology and ²Department of Pathophysiology and Therapeutics, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan.

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Correspondence: Michihiro Hide, MD PhD, Department of Dermatology, Integrated Health Sciences, Institute of Biomedical & Health Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan.

Email: ed1h-w1de-road@hiroshima-u.ac.jp

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INTRODUCTION

Hydrolyzed wheat protein (HWP) is obtained by hydrolyzing wheat with acids or enzymes. Because of its non-irritating and long-lasting foaming activity, HWP is widely used for numerous kinds of soaps, shampoos, creams, etc.^{1,2} instead of chemical foaming compounds. Recently, cases of wheat allergy caused by HWP¹⁻³ have been reported. Snegaroff *et al.*³ reported that some cases developed as wheat-dependent exercise-induced anaphylaxis (WDEIA). In Japan, many cases have been reported concerning patients who developed WDEIA after the use of HWP-containing soap,^{4,7} and all of the patients reported to date have used the same product (A case of HWP-WDEIA¹⁵ sensitized to HWP regarding another brand of soap was reported after the first publication of this article.).

In our hospital, the number of patients with WDEIA has greatly increased since 2010 and most cases had histories of HWP-containing soap usage. In this study, we report clinical characteristics, results of examinations, managements, and clinical courses of patients with WDEIA who visited our hospital in 2010 and 2011.

METHODS

SUBJECTS

Patients, who were diagnosed as WDEIA in Hiroshima University Hospital within 18 months (from January 2010 to June 2011), were evaluated, retrospectively. We classified WDEIA into two groups, one was a hydrolyzed wheat protein-WDEIA (HWP-WDEIA) group who had used HWP-containing soap before the development of WDEIA, and another was a conventional WDEIA (Co-WDEIA) group who had not used soap or cosmetics containing HWP. The diagnosis of WDEIA was made if a patient had a history of one or more incidences of anaphylaxis, and/or two or more allergic symptoms, after exercise, and showed a positive result in clinical examinations for wheat allergy, including, skin prick test, antigen-specific IgE, and histamine release test.

METHODS

From interview sheets and charts, we checked age, sex, use of HWP-containing soap, past history (especially about allergic diseases), clinical symptoms (face symptoms, urticaria, angioedema, respiratory symptoms, abdominal symptoms, and blood pressure reduction), and its onset, history of hospitalization, and use of epinephrine.

The minimum quantity of exercise to develop symptoms was classified as grade 1: daily living activities such as bathing or housekeeping; grade 2: light exercise, such as walking or shopping; grade 3: jogging or other sports.

Clinical symptoms were classified as grade 1: only

skin symptoms; grade 2: anaphylaxis of non-cutaneous organs without reduction of blood pressure; grade 3: anaphylaxis accompanying a reduction of blood pressure.

Skin prick tests (SPT) for wheat and bread were examined using prick lancets (Yayoi Co., Ltd., Tokyo, Japan) and allergen scratch extracts (Torii Pharmaceutical Co., Ltd., Tokyo, Japan). The response was classified as semi-positive (\pm), positive (+), when they were >25%, 50%, respectively, of the positive control response induced by histamine chloride at 10 mg/ml,⁷ negative when the average wheal diameters were the same as those of the negative control (saline), or smaller than those of semi-positive after 15 minutes.

We collected data of the specific IgE against wheat, gluten, and omega-5 gliadin (Imuno-CAP[®] Phadia AB, Uppsala, Sweden).

For histamine release tests (HRT), basophils were obtained from the peripheral blood of patients and were incubated with antigens. We defined % histamine release as (histamine released into the buffer)/(total histamine). We defined as positive if net % histamine release (difference between % histamine release in response to antigens and that in buffer) was 5% or more. Basophils were stimulated by gliadin-mix (TCI, Tokyo, Japan), glutenin-mix (TCI), omega-5 gliadin⁸ and HWP (Glupal-19S) (Katayama Chemical, Inc., Osaka, Japan) contained in the soap used by patients. Since we obtained HWP in May 2010, we performed HRT against HWP only when patients revisited our hospital after stopping the use of HWP-containing soap, except for one patient who first visited our hospital in June 2010.

All analyses were performed using Graph Pad Prism 5 (Graph Pad Software, San Diego, CA, USA).

This study was approved by the Ethics Committee of the Hiroshima University (No. 445).

RESULTS

CLINICAL CHARACTERISTICS OF PATIENTS WITH WDEIA-DEMOGRAPHY- (Table 1)

We diagnosed 40 patients as WDEIA, and 36 of them were checked for whether they had used the HWP-containing soap or not.

Among the 36 patients, 30 patients were diagnosed as HWP-WDEIA, 4 patients as Co-WDEIA, and 2 patients were unclassified because of uncertain histories. The HWP-containing soap used by the patients was the product of a company (Cha-no-Shizuku[®], Yuhka, Fukuoka, Japan).

All patients with WDEIA consisted of 7 males and 33 females, and the mean age was 37.6 years old (male 24, female 40.5).

The patients with HWP-WDEIA consisted of 2 males and 28 females, and their mean age was 40.3 \pm 16.9 years old. The mean age of 2 males and 2 females with Co-WDEIA was 36.8 \pm 6.2 years old.

Table 1 Clinical characteristics of patients with WDEIA -Demography-

	HWP-WDEIA	Co-WDEIA
Number of patients	30	4
Average of age (years)	40.3 (15-75) [†]	36.8 (30-43) [†]
Gender (Male : Female)	2 : 28	2 : 2
Use periods of HWP-soap by the onset (months)	12.8 (0.5-48)	none
Total use periods of HWP-soap (months)	18.1 (1-60)	none
Complication of eczema (History of eczema)	6/30 (10/30)	0/4 (1/4)

[†] Range of age; WDEIA, wheat-dependent exercise-induced anaphylaxis; HWP-WDEIA, hydrolyzed wheat protein-WDEIA; Co-WDEIA, conventional WDEIA.

Duration of the use of HWP-containing soap among 29 patients with HWP-WDEIA was from less than one month to 48 months and the average was 12.8 ± 13.1 months.

Regarding complication of other allergic diseases with HWP-WDEIA, six patients (4) suffered from atopic dermatitis, 2 (4), 4 (4), and 3 (2) patients were suffering from asthma, allergic rhinitis and allergic conjunctiva, respectively (the numbers in parenthesis mean the number of patients with respective complications only in the past history). In patients with Co-WDEIA, only one out of four patients had a past history of atopic dermatitis.

CLINICAL SYMPTOMS OF PATIENTS WITH WDEIA

Symptoms of patients with HWP-WDEIA were as follows: urticaria 27/30 (90.0%), angioedema 22/29 (75.8%), respiratory symptoms 22/28 (78.6%), facial symptoms 18/30 (60.0%), decreases of blood pressure 11/28 (39.3%), abdominal symptoms 7/30 (23.3%).

Six patients needed hospitalization and 3 patients had taken an injection of epinephrine.

We could evaluate the minimum quantity of exercise in 26 patients with HWP-WDEIA (grade 1: 6, grade 2: 15, grade 3: 5). Those in patients with Co-WDEIA were grade 2 in two patients and grade 3 in one patient.

Durations of symptoms in patients with HWP-WDEIA tended to be longer than those in patients with Co-WDEIA. In patients with HWP-WDEIA, 10 out of 24 patients suffered from symptoms for more than 3 to 4 days in each attack, eight patients for 2 hours to 1 day, and six patients for 2 hours or less. Durations of symptoms were confirmed in two patients with Co-WDEIA, and those of both patients were less than 2 hours.

Table 2 Clinical characteristics of patients with WDEIA -Symptoms and skin reactions in prick test-

	HWP-WDEIA	Co-WDEIA
Urticaria	27/30 (90%)	4/4 (100%)
Angioedema	22/29 (76%)	1/3 (33%)
Respiratory symptom	22/28 (79%)	2/2 (100%)
Face flash or itchy	18/30 (60%)	1/4 (25%)
Blood pressure reductions	11/28 (39%)	2/3 (67%)
Abdominal symptom	7/30 (23%)	1/3 (33%)
Skin prick test	Wheat (Torii)	18/22 (82%)
	Bread (Torii)	17/22 (77%)
		2/2 (100%)
		3/3 (100%)

WDEIA, wheat-dependent exercise-induced anaphylaxis; HWP-WDEIA, hydrolyzed wheat protein-WDEIA; Co-WDEIA, conventional WDEIA

SKIN PRICK TEST

Patients with HWP-WDEIA presented high positive rates of skin prick test for wheat 18/22 (81.8%), bread 17/22 (77.8%), but three patients were negative for both antigens (Table 2).

MEASUREMENT OF ANTIGEN-SPECIFIC IgE IN PATIENTS WITH HWP-WDEIA

The antigen-specific IgE in patients with HWP-WDEIA were as follows; wheat-specific IgE (CAP-WEIA): class 2 or more 23/30 (76.7%), class 1 or more 27/30 (90.0%); gluten-specific IgE (CAP-GEIA): class 2 or more 26/30 (86.7%), class 1 or more 29/30 (96.7%); omega5-gliadin-specific IgE (CAP-GEIA): class 2 or more 1/29 (3.4%), class 1 or more 4/29 (13.8%) (Fig. 1A). The levels of omega5-gliadin-specific IgE were statistically lower than those of the other wheat antigens (one-way ANOVA, $P < 0.05$) (Fig. 1B). The levels of gluten-specific IgE tended to be high in correlation with the grade of symptoms. However, there was no statistical difference among gluten-specific IgE of patients in each clinical grade (one-way ANOVA) (Fig. 2), presumably due to a large dispersion of the values of specific IgE. The numbers of peripheral blood eosinophil and total IgE were 3.5% (1.1-13.3%) and 357.6 IU/ml (41.6-2459 IU/ml) on average, respectively.

HISTAMINE RELEASE TEST (HRT) OF BASOPHILS FROM PATIENTS WITH HWP-WDEIA

HRTs against wheat allergens were performed in 28 patients with HWP-WDEIA. Four out of 28 patients were low-responders (net % histamine release against anti-IgE was less than 5%) and they were excluded from the analysis of positive rates in HRTs. Out of 24 patients (excluded low-responders), 11 (45.8%), 17 (70.8%) and four (16.7%) patients were positive when stimulated by gliadin-mix, glutenin-mix and omega5-gliadins, respectively, indicating glutenin as a major antigen. The negative rates of reaction to omega5-gliadin was statistically higher than those to the other

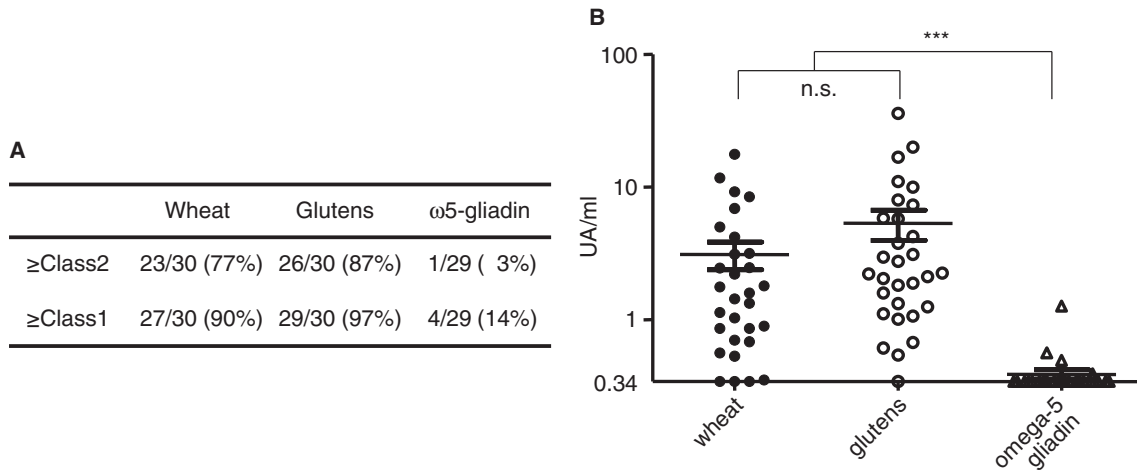


Fig. 1 Serum antigen-specific IgE levels with HWP-WDEIA. (A) Positive rate of specific IgE against wheat antigens. (B) Levels of antigen-specific IgE against wheat and those against glutens were significantly higher than those against omega-5 gliadin. Values less than 0.34 were accounted as 0.34 UA/ml for statistical calculations. WDEIA, wheat-dependent exercise-induced anaphylaxis; HWP-WDEIA, hydrolyzed wheat protein-WDEIA; *** $P < 0.001$, one way ANOVA.

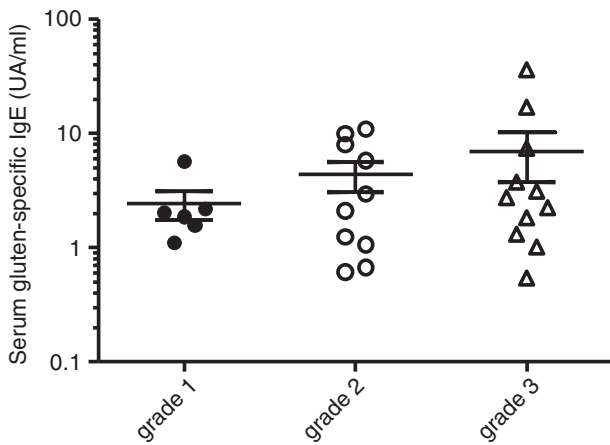


Fig. 2 Relation between serum gluten-specific IgE levels and grades of clinical symptoms in patients with HWP-WDEIA. Mean levels of gluten-specific IgE in grade 3 is the highest among 3 groups. There was no statistical difference among 3 clinical groups (One-way ANOVA). Grade 1: Patients had only skin symptoms, Grade 2: Patients had anaphylaxis symptoms, but not blood pressure reduction. Grade 3: Patients had histories of anaphylactic shock. WDEIA, wheat-dependent exercise-induced anaphylaxis; HWP-WDEIA, hydrolyzed wheat protein-WDEIA.

wheat antigens (one-way ANOVA, $P < 0.05$) (Fig. 3A, B).

HRTs against HWP were performed in 16 patients with HWP-WDEIA. All of them were positive, except for one low-responder patient (Fig. 3C, D). On the other hand, all patients with Co-WDEIA (2), atopic

dermatitis (4), cholinergic urticaria (1) were negative in reactions to HWP (data not shown).

GLUTEN-SPECIFIC IgE AND PERIODS USING HWP-SOAP (Fig. 4)

Levels of gluten-specific IgE were weakly correlated with periods using HWP-soap ($n = 29$).

CHANGES OF HWP-HYPERSENSITIVITIES IN PATIENTS WITH HWP-WDEIA AFTER THE DISCONTINUATION OF HWP-SOAP USAGE

We could follow up gluten-specific IgE in 11 patients with HWP-WDEIA over subsequent months. Levels of gluten-specific IgE antibodies had slowly decreased after stopping the use of HWP-soap (Fig. 5A).

The ratio of net % histamine release in response to glutenin-mix over that of anti-IgE had significantly decreased after three months since stopping the use of HWP-containing soap ($P < 0.05$, Fig. 5B). HRT against three wheat antigens became completely negative in one of the six patients. We therefore had permitted her to take wheat and do exercise. She had one slight attack (mild angioedema and respiratory discomfort) when she exercised after eating some bread two weeks after the permission had been given. The symptoms were promptly cleared by taking an antihistamine. In the following five months, she did not suffer from any symptoms upon consuming wheat and exercising.

In total 12 patients revealed a decrease of wheat hypersensitivity represented by gluten-specific IgE or HRTs. Nine of them had been prohibited to eat wheat-containing food when they took oral NSAIDs

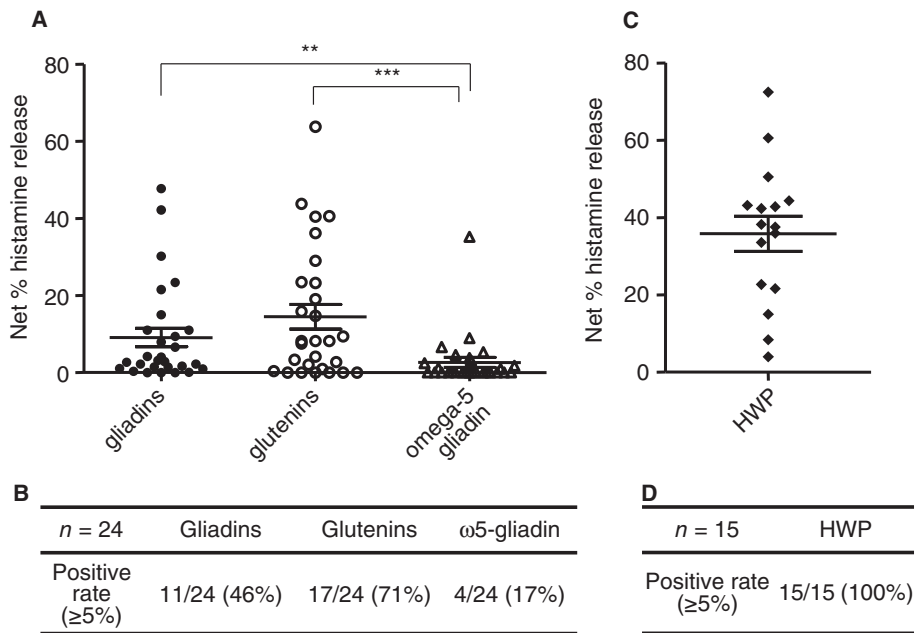


Fig. 3 Histamine release tests in patients with HWP-WDEIA. **(A)** Histamine release in response to gliadins and that to glutenins were significantly higher than that against omega-5 gliadin ($n = 28$). $**P < 0.01$, $***P < 0.001$, one way ANOVA. **(B)** Positive rate of histamine release test against wheat antigens in patients with HWP-WDEIA. We defined $\geq 5\%$ Net %histamine release as positive. The patients who had low response against anti-IgE ($< 5\%$) were excluded from statistical calculations. **(C)** Histamine release against HWP containing soap that HWP-WDEIA patients used ($n = 16$). Although some patients were already stopped the use of HWP-containing soap, levels of net% histamine release against HWP were still extremely high. **(D)** Positive rate of histamine release test against HWP in patients with HWP-WDEIA. All patients showed positive responses against HWP. We defined $\geq 5\%$ Net %histamine release as positive. The patients who showed low responses against anti-IgE ($< 5\%$) were excluded from statistical calculations. WDEIA, wheat-dependent exercise-induced anaphylaxis; HWP-WDEIA, hydrolyzed wheat protein-WDEIA; HWP, hydrolyzed wheat protein.

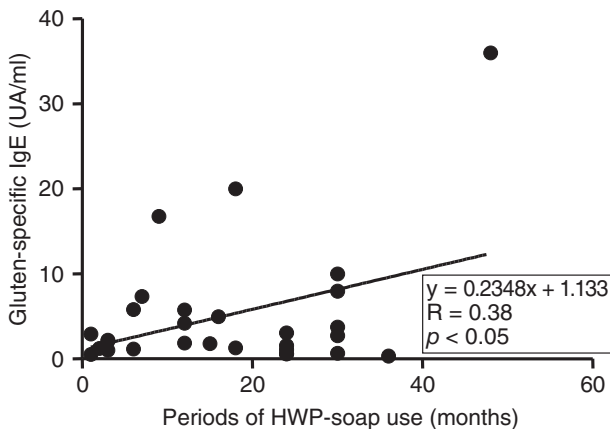


Fig. 4 Gluten-specific IgE antibodies and periods of HWP-soap use ($n = 29$). Levels of gluten-specific IgE were weakly correlated with periods of HWP-soap use. Values less than 0.34 were calculated as 0.34 UA/ml for statistical calculations. HWP, hydrolyzed wheat protein.

or exercise, but had been permitted to consume small amounts of wheat when they were resting. One patient consumed substantial amounts of wheat once a month and the other two patients were completely restricted from consuming wheat.

DISCUSSION

In this study, we demonstrated among our patients that: 1. The number of the patients with WDEIA increased and most of them were HWP-WDEIA; 2. the patients with HWP-WDEIA were mostly women, and older than the patients with Co-WDEIA; 3. the level of gluten-specific IgE tended to be high, and omega-5 gliadin tended to be low; 4. the same tendency was observed for HRT; 5. levels of gluten-specific IgE were weakly correlated with periods of HWP-containing soap usage; 6. the wheat-hypersensitivity of patients with HWP-WDEIA tended to decrease after stopping the usage of HWP-containing soap over months and could possibly be cured.

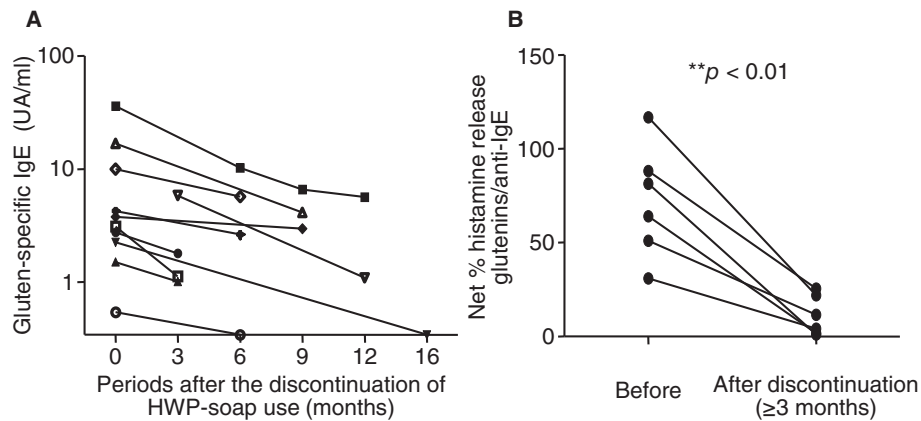


Fig. 5 Changes of HWP-hypersensitivities in patients with HWP-WDEIA after the discontinuation of HWP-soap use. **(A)** Levels of gluten-specific IgE antibodies decreased after stopping the use of HWP-soap ($n = 11$). **(B)** Histamine release in response to glutenins before and after the discontinuation of HWP-soap ($n = 6$). WDEIA, wheat-dependent exercise-induced anaphylaxis; HWP, hydrolyzed wheat protein.

The number of patients with food-dependent exercise-induced anaphylaxis (FDEIA) who visited our hospital during a one year and six month period (from January 2010 to June 2011) was 46. In contrast, only five patients visited our hospital during an earlier 1 year and eight month period (from December 2003 to July 2005).⁹ This observation indicated that the number of the patients with FDEIA had considerably increased recently. Moreover, the rate of WDEIA among FDEIA 87% (40/46) was larger than a previous report of Mochizuki, *et al* (57%).¹⁰

Hisamoto¹¹ reported that the mean age of 68 patients with FDEIA was 20.1 years, and that 48 (70.6%) were male and 20 (29.4%) were female. In our study, mean age of 46 patients with FDEIA was 37.6 years, and the numbers of male and female were 9 and 37, thus, relatively older and a higher rate being female. At first, we were not aware of the reason for such an increase in females, and age of patients with WDEIA. However, publications of similar reports about HWP-WDEIA in Japan prompted us to interview the patients about the use of particular soaps, resulting in the demonstration of a high rate (83.3% of whole WDEIA patients) of HWP-containing soap usage among the patients.

Many patients with HWP-WDEIA in our hospital had developed symptoms of face and angioedema, but the number of patients who had suffered from reduction of blood pressure and abdominal symptoms was small. Chinuki *et al.*¹² reported that the main symptoms of Co-WDEIA and HWP-WDEIA were urticaria (wheal) and angioedema (especially eyelids), respectively. They also reported that patients with Co-WDEIA experienced anaphylactic shock more often than patients with HWP-WDEIA. Another clinical difference between HWP-WDEIA and Co-WDEIA was the amount of exercise to evoke attacks. Six pa-

tients (22.2%) with HWP-WDEIA experienced attacks even after domestic work or taking a bath. Thus the symptoms of HWP-WDEIA may be induced easily by light exercise as compared with those of Co-WDEIA. Regarding the duration of attacks, those in patients with HWP-WDEIA tended to be longer (3-4 days in 41.7% patients), possibly due to the complication with angioedema.

SPT for wheat and bread were positive in 81.8% and 77.2% in patients with HWP-WDEIA, respectively. Namely, SPT was false negative in 18.2% patients with HWP-WDEIA. Most patients with HWP-WDEIA were negative in Immuno-CAP[®] for omega-5 gliadin-specific IgE. Even if omega-5 gliadin-specific IgE was positive, the levels of wheat- and gluten-specific IgE were higher than that of omega-5 gliadin-specific IgE. Fukutomi⁴ and Chinuki⁷ also pointed out that the levels of omega-5 gliadin-specific IgE were almost negative in patients with HWP-WDEIA. Therefore, positive wheat- and gluten-specific IgE and negative omega-5 gliadin-specific IgE may be taken as a proof to distinguish HWP-WDEIA from Co-WDEIA.

In accordance with antigen-specific IgE, histamine release in response to gliadins and glutenins were significantly higher than that to omega-5 gliadin. Even if patients had a positive response to omega-5 gliadin, the levels of histamine release were lower than that to glutenins in all cases. HRTs against HWP were all positive except for one low-responder. These results suggest that patients with HWP-WDEIA were sensitized by HWP rather than by natural wheat.

One patient was entirely negative in SPT and antigen-specific IgE, but was positive in HRT against glutenins and omega-5 gliadin. Therefore, we diagnosed him as HWP-WDEIA with consideration of both positive HRT and his clinical history. In contrast, another patient was negative in SPT and a low-

responder in HRT, but both wheat- and gluten-specific IgE were positive. We diagnosed her as HWP-WDEIA with consideration of the detection of specific IgE by Immuno-CAP[®] and her clinical history. These results suggested that the importance of conducting multiple tests, especially when WDEIA was suspected based on their history, but a particular test gave a negative result against wheat and its components.

To clarify the relationship between the use of HWP-containing soap, and the onset of WDEIA, and/or their clinical data, we analyzed the correlation between the duration of HWP-soap usage and levels of gluten-specific IgE by regression analysis. It revealed that these factors were weakly, but significantly correlated ($P < 0.05$). Fukutomi *et al.*⁴ reported that the binding of specific IgE in sera from patients with HWP-WDEIA to HWP was fully inhibited by HWP, but not by natural wheat extracts. In our study, basophils from patients with HWP-WDEIA reacted substantially more strongly with HWP than that with other natural wheat antigens. These observations suggested that patients with HWP-WDEIA were previously sensitized to HWP via skin and mucosa by being exposed to HWP-containing soap. Chinuki *et al.*⁷ speculated that one of the reasons for sensitization to HWP by the usage of HWP-containing soap was due to destruction of skin barrier function by detergents contained in the soap. Although they reported that only one out of 12 patients with HWP-WDEIA was complicated with atopic dermatitis, six out of 30 (20%) patients had been suffering from atopic dermatitis in this study. Taking into account that the prevalence of atopic dermatitis in Japan was 2.5% in the 50 to 59 year age group, 4.8% in 40 to 49 year age group, 8.3% in 30 to 39 year age group and 9.4% in 20 to 29 year age group,¹³ patients with atopic dermatitis may be susceptible to the development of HWP-WDEIA.

Information about clinical course of wheat allergy in adult onset, including Co-WDEIA, was limited, especially about remission. Our data on the decreases of wheat-hypersensitivities in patients with HWP-WDEIA after the discontinuation of HWP-soap usage not only suggest the relation between the usage of HWP-containing soap and the onset of HWP-WDEIA, but also imply the possibility of improvement of such hypersensitivity against wheat. In our hospital, we recommend that patients with HWP-WDEIA avoid the combination of wheat and exercise rather than complete avoidance of wheat products. Nine out of 12 patients with gluten-specific IgE and/or the reactivity against glutenin in HRT continued to eat small amounts of wheat and decreased their sensitivities. We could not find a significant difference of remission rate of wheat-hypersensitivity between the group with complete avoidance of wheat and that with continuous taking of small amounts of wheat. It is feasible that continuous intake of wheat might have led a

tolerance rather than allergy.¹⁴ Reports from multiple institutions are needed to clarify the influence of oral intake of wheat on the hypersensitivity against wheat after the discontinuation of HWP-soap usage.

All patients with HWP-WDEIA in this study and previously reported in Japan had used the same kind of soap (Cha-no-Shizuku[®]). However, this HWP (Glupal-19S) had also been contained in many other cosmetics of other companies. The reason why there are no reports about other cosmetics is unclear (A case of HWP-WDEIA¹⁵ sensitized to HWP regarding another brand of soap was reported after the first publication of this article.). Since as many as forty-six million bars of Cha-no-Shizuku[®] were sold in Japan from 2004 to 2010, it may be simply due to such a very large number of people exposed to this soap. Alternatively, the composition of other ingredients and the way of using the soap might also be important and should be a subject for investigation. The company that sold Cha-no-Shizuku[®] has launched a self-imposed recall of the item and excluded HWP from the new lots of this soap. Moreover, the company that made Glupal-19S has already stopped making and distributing HWP. Therefore, the number of patients with HWP-WDEIA is expected to decrease in the future. However, since other types of HWP are still contained in many products such as cosmetics and foods, further analysis is needed to clarify whether only Glupal-19S among HWPs have a sensitizing capacity or other HWPs could also have such activity.

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