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Original article

Better management of wheat allergy using a very low-dose food challenge: A retrospective study

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EAACI	European Academy of Allergy and Clinical Immunology
OFC	Oral food challenge
OIT	Oral immunotherapy
VL	Very low-dose

ABSTRACT

Background: Low-dose reactive wheat-allergic children are at a high risk of a positive oral food challenge (OFC). The present study aimed to evaluate whether the results of a very low-dose (VL) OFC would contribute to better wheat allergy management in this population.
Methods: We retrospectively reviewed wheat-allergic subjects who underwent a VL OFC with 2 g of udon noodles (equivalent to 53 mg of wheat protein) and had a previous allergic reaction to <15 g of udon noodles (equivalent to 400 mg of wheat protein) within 2 years before the OFC. Subjects who passed the OFC were defined as VL tolerant; those who failed were considered VL reactive. In VL tolerant subjects, the dose was increased to 15 g of udon noodles either during an OFC in our hospital or gradually at home.
Results: Of the 57 included subjects (median age, 2.9 years; range, 1.0–11.8 years), 32 (56%) were VL tolerant and 25 (44%) were VL reactive. Most reactions during the OFC could be treated with an antihistamine and/or a nebulized β2 agonist. VL tolerant subjects consumed 2 g of udon noodles or a seasoning containing wheat. Within a year after the OFC, 18 VL tolerant subjects (56%), but no VL reactive subjects, were able to consume 15 g of udon noodles ($p < 0.001$).
Conclusions: A VL OFC can shift the management of some low-dose reactive wheat-allergic children from complete avoidance to partial wheat intake.

Introduction

Immunoglobulin (Ig) E-mediated wheat allergy is the third-most common food allergy in Japan.[1] A review of the natural history of wheat allergy reported that 29%, 56%, and 65% of children outgrow such allergies by age 4, 8, and 12 years, respectively.[2,3] However, many children continue to suffer from wheat allergy, and an oral food challenge (OFC) is therefore needed to assess the achievement of tolerance.[4] These challenges must be conducted carefully in low-dose reactive wheat-allergic children, who are at a high risk of a positive OFC and react severely to high-dose intakes.[5,6]

Oral immunotherapy (OIT), which reportedly contributes to desensitization or threshold elevation in wheat-allergic children,[7,8] is a possible approach for the management of wheat allergy. However, this process might be impractical or inconvenient in real life because of the need for daily ingestion and risk of possible adverse reactions.[9]

Baked egg and baked milk have been used as approaches for the management of hen egg allergy and cow's milk allergy, respectively.[10,11] On the other hand, wheat is usually consumed in a cooked form, and allergenicity was not found to differ significantly between raw and cooked forms of wheat.[12]

We previously reported that a very low-dose (VL) OFC with cow's milk provided better management in patients with low-dose reactive cow's milk allergy.[13] Therefore, we decided to test a VL OFC with wheat for wheat allergy. To determine whether a VL OFC with wheat was as effective for wheat allergy as a VL OFC with cow's milk for cow's milk allergy, we performed a VL OFC (2 g of udon noodles, equivalent to 53 mg of wheat protein) and wheat dose progression in wheat-allergic children who had experienced a previous reaction to <15 g of udon noodles (equivalent to 400 mg of wheat protein) based on our daily practice.

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Methods

Study design

We retrospectively reviewed subjects with low-dose wheat reactions who underwent a VL OFC involving 2 g of udon noodles. Subjects who passed the VL OFC were defined as VL tolerant, and those who failed the VL OFC were defined as VL reactive.

The results of the VL OFC are presented as the OFC positive rate, as well as symptoms and treatments administered during the OFC. The results of the wheat dose progression in our daily practice during a 1-year period after the OFC were compared between the VL tolerant and VL reactive subjects according to the time needed to reach an intake of 15 g of udon noodles.

Informed consent for the OFC and data publication was obtained from the children's guardians. This study was approved by the Sagamihara National Hospital Ethics Committee and was conducted in accordance with the Declaration of Helsinki. The research plan was posted at Sagamihara National Hospital. However, because this study was retrospective, registration in an internationally certified registry was not required.

Subject selection

The eligible subjects were children who underwent VL OFC between July 2012 and January 2014, had a previous allergic reaction to <15 g of udon noodles within the 2 years before the VL OFC (median, 9.3 months; range, 1.5–23.2 months), and had a positive wheat-specific IgE test result. Previous allergic reactions were defined as immediate reactions if they occurred within 2 h after ingesting wheat. Worsening of eczema or asthma after ingesting wheat was not included in the immediate reactions. If previous allergic reactions occurred because of accidental ingestion, wheat doses were calculated using a conversion table constructed by the research dieticians.

Assessment of baseline characteristics

The attending physician was responsible for diagnoses of food allergies, eczema, asthma, and allergic rhino-conjunctivitis. Anaphylaxis was defined according to the criteria proposed by Simons *et al.*[14]

Laboratory testing

For all subjects, wheat-specific IgE levels were assessed using the ImmunoCAP assay system (Thermo Fisher Scientific, Uppsala, Sweden), and a level >0.35 kilounits of allergen-specific IgE (kUA)/L was considered positive. The median time between the laboratory test and VL OFC was 3.2 months (range, 0.0–18.4 months).

Oral food challenge protocol

The challenge food used in the VL OFC was 2 g of udon noodles (equivalent to 53 mg of wheat protein). Udon noodles are a traditional Japanese food prepared by boiling a mixture of wheat flour, water, and salt for 1 min.

OFCs were performed openly under physician observation at Sagamihara National Hospital. One quarter of the VL OFC challenge food was administered initially, and the remaining three quarters were administered 60 min later. The OFC was concluded when a quantity of wheat sufficient to cause moderate or severe symptoms (generalized urticaria, continuous coughing, moderate or severe abdominal pain, vomiting, or diarrhoea) had been consumed. If mild objective symptoms (localized urticaria or intermittent coughing) appeared during the OFC, the subject was carefully monitored to detect any worsening of symptoms. If the mild objective symptoms disappeared within 30 min, the OFC was continued. When an adverse reaction occurred, treatment (antihistamine, nebulized β2 agonist, steroids, or adrenaline) was administered based on the European Academy of Allergy and Clinical Immunology (EAACI) food allergy and anaphylaxis guidelines.[15]

Wheat dose progression and follow-up

Subjects who passed the VL OFC were advised to consume 2 g of udon noodles or a seasoning containing wheat at least once weekly while at home. One to 3 months after passing the OFC, the wheat dose was increased to 15 g of udon noodles either during an OFC at our hospital or gradually at home. With the latter method, the udon noodle dose was increased by 1 g every few ingestions. If adverse reactions appeared, the previous dose was repeated. When the previous dose was passed, the scheduled increase was attempted. Subjects who failed the VL OFC underwent a second OFC at least 6 months after the first OFC.

We prescribed antihistamines for all subjects, adrenaline autoinjectors for subjects with a history of anaphylaxis, and other medications depending on complications. All subjects received instructions on when and how to administer emergency medications and visit the emergency department.

Statistical analysis

Characteristics at the time of the VL OFC were compared between the VL tolerant and VL reactive subjects, as well as between VL tolerant subjects who achieved a dose of 15 g of udon noodles (15 g tolerant) and VL tolerant subjects who failed an OFC with 15 g of udon noodles (15 g reactive) within 1 year after the VL OFC using the Mann–Whitney test for continuous variables (expressed as medians and ranges) and the chi-square or Fisher's exact test for categorical variables (expressed as numbers and percentages).

Wheat dose progression was measured as the time required to reach the consumption of 15 g of udon noodles. Kaplan–Meier curves were generated to depict changes among the VL tolerant and VL reactive subjects. Differences were estimated using the log-rank test.

SPSS version 20 (IBM Corp, Armonk, NY, USA) was used for all analyses.

Results

Baseline subject characteristics

Of the 83 subjects who underwent the VL OFC between July 2012 and January 2014, 23 subjects were excluded for a previous allergic reaction to wheat more than 2 years prior, and 3 were excluded for a previous reaction to >15 g of udon noodles within the previous 2 years; a total of 57 subjects (median age, 2.9 years; range, 1.0–11.8 years) remained in the analyses (Fig. 1). The median wheat-specific IgE level was 26.9 kUA/L (range, 0.63–1520 kUA/L), and the median ω5-specific IgE level was 1.5 kUA/L (range, <0.10–65.3 kUA/L) (Table 1). Of the baseline subject characteristics, the VL tolerant (n = 32, 56%) and VL reactive (n = 25, 44%) subjects differed significantly with regard to a history of anaphylaxis to wheat, wheat-specific IgE levels, and ω5-specific IgE levels (Table 1).

The subjects' previous allergic reactions had been caused by accidental ingestion (56%) or an OFC with wheat (44%). The median threshold dose at the previous OFC with wheat was 8.0 g (range, 2.0–15.0 g) of udon noodles (Table 2). The threshold dose in the previous OFC with wheat was higher among VL tolerant subjects

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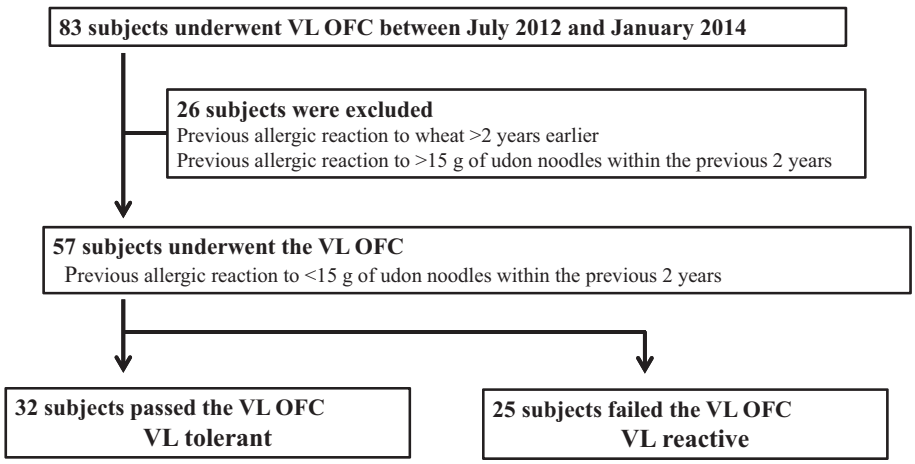

Fig. 1. Flowchart of enrolled subjects in an assessment of the usefulness of an oral food challenge (OFC) for wheat allergies. The very low-dose (VL) OFC was conducted with 2 g of udon noodles (equivalent to 53 mg of wheat protein). In this study, 15 g of udon noodles were considered equivalent to 400 mg of wheat protein.

Table 1
Baseline characteristics of subjects with wheat allergies who underwent a very low-dose oral food challenge.

Characteristic	All subjects (n = 57)	VL tolerant (n = 32)	VL reactive (n = 25)	*p* value*
Age (years)	2.9 (1.0–11.8)	2.0 (1.0–11.8)	3.8 (1.3–6.8)	0.150
Male sex	35 (61)	20 (63)	15 (60)	0.847
History of anaphylaxis to wheat	26 (46)	10 (31)	16 (64)	**0.014**
Other food allergy, current	48 (84)	25 (78)	23 (92)	0.145
Eczema, current	36 (63)	23 (72)	13 (52)	0.123
Asthma, current	18 (32)	8 (25)	10 (40)	0.227
Allergic rhino-conjunctivitis, current	7 (12)	3 (9.4)	4 (16)	0.360
Total IgE (kUA/L)	448 (45.6–5510)	432 (45.6–3050)	490 (53.1–5510)	0.817
Wheat-specific IgE (kUA/L)	26.9 (0.63–1520)	15.0 (0.63–72.1)	42.2 (7.5–1520)	**<0.001**
ω5-specific IgE (kUA/L)	1.5 (<0.10–65.3)	0.81 (<0.10–11.9)	5.8 (0.15–65.3)	**<0.001**

*Comparisons between VL tolerant and VL reactive subjects were conducted using the Mann–Whitney test for continuous variables or the chi-square or Fisher's exact test for categorical variables. Statistically significant *p* values (<0.05) are in bold.
Values are reported as medians (ranges) or n (%).
VL, very low dose; IgE, immunoglobulin E; kUA/L, kilounits of allergen-specific IgE.

than among VL reactive subjects, and the rates of respiratory symptoms and anaphylaxis were lower among VL tolerant subjects than among VL reactive subjects (Table 2).

Results of the very low-dose oral food challenge

Respiratory symptoms were most common, occurring in 92% (n = 23) of the VL reactive subjects, followed by skin symptoms in 72% (n = 18) of the VL reactive subjects. The majority of reactions were treated with antihistamines and/or nebulized β2 agonists. Among the 23 subjects with respiratory symptoms, 16 (70%) received 1 dose of a nebulized β2 agonist, 4 (17%) received 2 doses of a nebulized β2 agonist, and 3 (13%) received 1 dose of adrenaline. The subject who received 1 dose of adrenaline for respiratory symptoms required another dose of adrenaline for mild hypotension (Table 3).

Wheat dose progression based on our daily practice within the year after the very low-dose oral food challenge

Of the VL tolerant subjects, 17 of 23 who underwent an OFC with 15 g of udon noodles passed the OFC. The remaining 9 VL tolerant

Table 2
Characteristics of previous allergic reactions to wheat.

Characteristic	All subjects (n = 57)	VL tolerant (n = 32)	VL reactive (n = 25)	*p* value*
Reason for previous allergic reaction to wheat				
Accidental ingestion	32 (56)	15 (47)	17 (68)	0.111
OFC with wheat	25 (44)	17 (53)	8 (32)	
Threshold dose at previous OFC with wheat (g udon noodles)	8.0 (2.0–15.0) (n = 25)	15.0 (2.0–15.0) (n = 17)	7.0 (2.0–15.0) (n = 8)	**0.031**
Symptom during previous allergic reaction to wheat				
Skin	51 (90)	28 (88)	23 (92)	0.461
Gastrointestinal	9 (16)	3 (9.4)	6 (24)	0.128
Respiratory	30 (53)	13 (41)	17 (68)	**0.040**
Cardiovascular	2 (3.5)	0 (0.0)	2 (8.0)	0.188
Anaphylaxis	26 (46)	10 (31)	16 (64)	**0.014**

*Comparisons between VL tolerant and VL reactive subjects were conducted using the Mann–Whitney test for continuous variables or the chi-square or Fisher's exact test for categorical variables. Statistically significant *p* values (<0.05) are in bold.
Values are reported as medians (ranges) or n (%).
VL, very low dose; OFC, oral food challenge.
One gram of udon noodles is equivalent to 26.5 mg of wheat protein.

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Table 3
Symptoms and administered treatments during the very low-dose (VL) oral food challenge with wheat.

	VL reactive (n = 25)
Symptoms	
Skin (%)	18 (72)
Gastrointestinal (%)	7 (28)
Respiratory (%)	23 (92)
Cardiovascular (%)	1 (4.0)
Anaphylaxis (%)	13 (52)
Treatments	
Antihistamine (%)	21 (84)
β2 agonist, nebulized (%)	23 (92)
Steroids (%)	6 (24)
Adrenaline (%)	3 (12)

The VL reactive subjects failed a VL oral food challenge conducted with 2 g of udon noodles (equivalent to 53 mg of wheat protein).

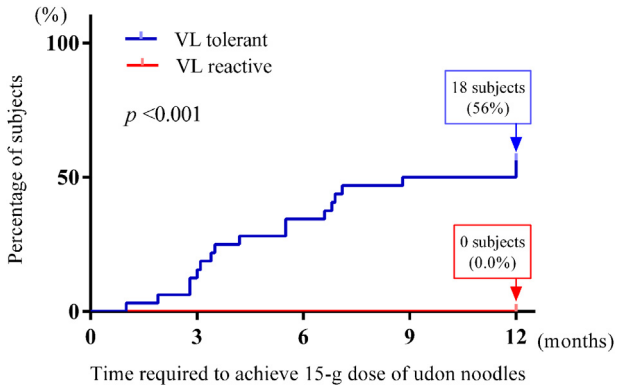

Fig. 2. Kaplan–Meier curves demonstrating the time required to achieve consumption of 15 g of udon noodles (equivalent to 400 mg of wheat protein) during a 1-year period after a very low-dose (VL) oral food challenge for wheat allergy.

subjects underwent gradual increases in their wheat doses at home, and 1 reached a 15-g dose of udon noodles. Therefore, a total of 18 (56%) VL tolerant subjects reached a dose of 15 g of udon noodles.

Of the VL reactive subjects, only 2 of 16 who underwent a second VL OFC passed this OFC. None (0.0%) of the VL reactive subjects reached a dose of 15 g of udon noodles ($p < 0.001$) (Fig. 2).

Table 4
Comparisons of baseline characteristics between VL tolerant subjects who reached a dose of 15 g of udon noodles (15 g tolerant) and VL tolerant subjects who failed an OFC with 15 g of udon noodles (15 g reactive) within 1 year after the VL OFC.

Characteristic	15 g Tolerant (n = 18)	15 g Reactive (n = 6)	*p* value*
Age (years)	2.0 (1.3–7.7)	5.6 (1.0–11.8)	0.317
Male sex	11 (61)	4 (67)	0.603
History of anaphylaxis to wheat	3 (17)	5 (83)	**0.007**
Other food allergy, current	14 (78)	5 (83)	0.634
Eczema, current	15 (83)	2 (33)	**0.038**
Asthma, current	4 (22)	3 (50)	0.215
Allergic rhino-conjunctivitis, current	3 (17)	0 (0)	**0.010**
Total IgE (kUA/L)	329 (85.8–3050)	362 (141–1160)	0.947
Wheat-specific IgE (kUA/L)	19.1 (0.63–72.1)	17.3 (1.8–40.3)	0.947
ω5-specific IgE (kUA/L)	0.70 (<0.10–11.9)	1.7 (0.15–5.67)	0.228

*Comparisons between 15 g tolerant and 15 g reactive subjects were conducted using the Mann–Whitney test for continuous variables or the chi-square or Fisher's exact test for categorical variables. Statistically significant *p* values (<0.05) are in bold.
Values are reported as medians (ranges) or n (%).
IgE, immunoglobulin E; kUA/L, kilounits of allergen-specific IgE.
Fifteen grams of udon noodles is equivalent to 400 mg of wheat protein.

Table 5
Comparisons of characteristics of previous allergic reactions to wheat between VL tolerant subjects who reached a dose of 15 g of udon noodles (15 g tolerant) and VL tolerant subjects who failed an OFC with 15 g of udon noodles (15 g reactive) within 1 year after the VL OFC.

Characteristic	15 g Tolerant (n = 18)	15 g Reactive (n = 6)	*p* value*
Reason for previous allergic reaction to wheat			
Accidental ingestion	9 (50)	2 (33)	0.410
OFC with wheat	9 (50)	4 (67)	
Threshold dose at previous OFC with wheat (g udon noodles)	15.0 (6.0–15.0) (n = 9)	11.5 (2.0–15) (n = 4)	0.598
Symptom during previous allergic reaction to wheat			
Skin	16 (89)	6 (100)	0.554
Gastrointestinal	3 (17)	0 (0)	0.403
Respiratory	4 (22)	5 (83)	**0.015**
Cardiovascular	0 (0)	0 (0)	
Anaphylaxis	3 (17)	5 (83)	**0.007**

*Comparisons between 15 g tolerant and 15 g reactive subjects were conducted using the Mann–Whitney test for continuous variables or the chi-square or Fisher's exact test for categorical variables. Statistically significant *p* values (<0.05) are in bold.
Values are reported as medians (ranges) or n (%).
OFC, oral food challenge.
Fifteen grams of udon noodles is equivalent to 400 mg of wheat protein.

When comparing the characteristics of VL tolerant subjects who achieved a dose of 15 g of udon noodles (15 g tolerant, n = 18) and those of VL tolerant subjects who failed an OFC with 15 g of udon noodles (15 g reactive, n = 6), the 15 g tolerant and 15 g reactive subjects showed significant differences with regard to current eczema, current allergic rhino-conjunctivitis, and a history of respiratory symptoms and anaphylaxis in response to wheat (Table 4, 5).

Adverse reaction to wheat consumed at home

A 2-year-old boy (3.1%) had 1 reactionary episode to 2 g of udon noodles. The boy had an intermittent cough at 1 month after the VL OFC. No subjects (0.0%) had any reactionary episodes to 3–15 g of udon noodles. None of the adverse reactions required adrenaline or a visit to the emergency department. There was no worsening of eczema or asthma (Table 6).

Discussion

To the best of our knowledge, this is the first study to indicate that a VL OFC with wheat could be useful for the management of low-dose reactive wheat-allergic children. Based on the OFC

Table 6
Adverse reactions to wheat at home after passing the very low-dose (VL) oral food challenge.

	VL tolerant	
	Very low-dose (2 g udon noodles) (n = 32)	Dose escalation (3–15 g udon noodles) (n = 32)
No. (%) of subjects	1 (3.1)	0 (0.0)
No. of adverse reactions	1	0
Skin	0	0
Gastrointestinal	0	0
Respiratory	1	0
Cardiovascular	0	0
Anaphylaxis	0	0

The VL tolerant subjects passed a VL oral food challenge conducted with 2 g of udon noodles (equivalent to 53 mg of wheat protein).
In this study, 3–15 g of udon noodles was equivalent to 80–400 mg of wheat protein.

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results, half of the children in the present study could begin consuming very low doses of wheat products on a daily basis. Furthermore, approximately half of these VL-tolerant children could consume 15 g of udon noodles within a year after the VL OFC.

We believe that our definition of low-dose reactivity to wheat is appropriate because a previous study used 9 g of wheat flour, equivalent to 900 mg of wheat protein, for a low-dose OFC[16]; we accordingly defined low-dose reactive wheat allergy based on a previous allergic reaction to <15 g of udon noodles, equivalent to 400 mg of wheat protein.

Wheat-specific and ω5-specific IgE levels, respiratory symptoms and anaphylaxis during a previous allergic reaction to wheat, and the threshold dose of a previous OFC with wheat were found to be predictors of VL OFC results, consistent with previous studies. Many previous studies reported that wheat-specific and ω5-specific IgE levels were predictive of the outcome of an OFC with wheat.[17–20] Nilsson *et al.* reported that respiratory symptoms during a previous allergic reaction were predictive of the results of an OFC with wheat.[20] Previous studies have not reported a predictive threshold for a previous OFC with wheat. However, our findings are compatible with those of our previous report, in which the threshold dose of a previous OFC with cow's milk was predictive of the results of a VL OFC with cow's milk.[13]

Although many of the VL reactive subjects experienced skin and respiratory symptoms during the VL OFC, these reactions were treatable with antihistamines and/or nebulized β2 agonists. Compared with subjects who underwent an OFC with wheat in a previous study, our subjects had higher levels of wheat-specific IgE (median of subjects who failed the OFC in the present study, 42.2 kUA/L vs. 19.9 kUA/L in the earlier study) but a lower rate of adrenaline treatment (12% vs. 18%).[21] Because of the high anaphylaxis rate, our use of adrenaline may appear inappropriate. However, many respiratory symptoms were equivalent to mild wheezing as defined in the EAACI taskforce position paper,[22] and most reactions were mild to moderate, even in low-dose reactive wheat-allergic children who failed the VL OFC.

Almost all VL tolerant subjects were able to safely consume less than 15 g of udon noodles at home. Burks *et al.* reported that in a placebo group, the adverse reaction rate was 3.9%.[23] As even placebos can cause adverse reactions to some extent, the adverse reaction rate to 2 g of udon noodles at home (3.1%) can be considered acceptable. Instead of a wheat OIT, low-dose reactive wheat-allergic children can begin to consume wheat through a VL OFC with wheat.

Compared with VL reactive subjects, VL tolerant subjects were more likely to have reached a 15-g dose of udon noodles. Previous studies reported that the wheat-specific IgE and ω5-specific IgE levels were predictive of the wheat allergy course.[2,24] Whether the VL OFC result is an independent predictor of the wheat allergy course is not evident because of the potentially confounding differences in wheat-specific IgE and ω5-specific IgE levels in the present study. However, Elizur *et al.* reported that a higher reaction threshold predicted the resolution of an allergy to cow's milk.[25] Therefore, the VL OFC result is a potential predictor of the wheat allergy course.

VL tolerant subjects did not necessarily achieve a 15-g dose of udon noodles. In the present study, current eczema, current allergic rhino-conjunctivitis, and respiratory symptoms and anaphylaxis during a previous allergic reaction to wheat were found to be negative predictors of tolerance to a 15-g dose of udon noodles. VL tolerant subjects with allergic comorbidities and/or a history of respiratory symptoms and anaphylaxis in response to wheat should be carefully observed.

One limitation of our study is that it was not evident whether the 8 VL tolerant subjects who underwent gradual increases in their wheat doses at home but did not achieve a 15-g dose of udon noodles, the 9 VL reactive subjects who did not undergo a second VL OFC, and the other 2 VL reactive subjects who passed a second VL OFC could ingest 15 g of udon noodles without any symptoms within 1 year after the VL OFC. However, if we presume that the same proportion of the 9 VL reactive subjects could have passed a second VL OFC and the VL reactive subjects who passed a second VL OFC could successfully ingest 15 g of udon noodles, the VL tolerant subjects were still more likely than the VL reactive subjects to have achieved tolerance to a 15-g dose of udon noodles.

In conclusion, VL OFC helps to identify low-dose reactive wheat-allergic children who might be able to shift from complete avoidance to partial intake of wheat, thus allowing better management. Additional studies are needed to determine whether the VL OFC result is predictive of the wheat allergy course.

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Conflict of interest

The authors have no conflict of interest to declare.

Author's contributions

YO performed research, analysed data, and wrote the paper. NY supervised YO's work. SS and ME contributed to the data analysis and preparation and revision of the manuscript.

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