ORIGINAL ARTICLE

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Safe egg yolk consumption after a negative result for low-dose egg oral food challenge

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Abstract

Background: Hen's egg is one of the most common allergens causing infantile food allergy. Consuming heated egg yolk slightly contaminated with egg white (EY with scEW) improves diet quality. Most children with egg allergies can safely consume 1/25 of a heated whole egg (low-dose egg). Although low-dose egg has similar antigenicity to EY with scEW, clinical reproducibility is unknown. We aimed to examine the safety of EY with scEW consumption after a negative result of low-dose egg oral food challenge (OFC).

Methods: In this prospective study, children aged <18 years with a history of immediate reaction to eggs were enrolled. We advised children and guardians to consume EY with scEW after a negative result of low-dose egg OFC and to record symptoms, if anv.

Results: We evaluated 276 children with negative results for low-dose egg OFC who had previously shown reactivity to eggs. Their median age was 1.2 years. Boys accounted for 188 (68%) of the children. The median egg white-specific immunoglobulin E level was 11.7 kU_A/L. At home, six children experienced mild symptoms. Skin symptoms were the most common. Among the six children, five were confirmed to continue the consumption of EY with scEW and one developed mild respiratory symptoms and continued to avoid eating eggs.

Conclusion: Although a few children with egg allergies experience mild symptoms, most of them can ultimately consume EY with scEW. Consumption of EY with scEW after low-dose egg OFC seems safe and may improve their quality of life by making egg yolk products available.

KEYWORDS

child, egg, egg yolk, food allergy, oral food challenge

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1 | INTRODUCTION

Hen's egg is one of the most common allergens for infantile food allergy.^{1,2} Among infants in Western countries, the estimated prevalence rate of egg allergy is around 2%.^{3,4} The major allergens in eggs are ovalbumin and ovomucoid,⁴ and egg volk products include a little egg white containing ovalbumin and ovomucoid.⁵ Oral food challenges (OFCs) with heated egg yolk can help most children with egg allergies to consume products containing heated egg yolk slightly contaminated with egg white (EY with scEW) safely (e.g., cookies, seasoning, and bread),⁵ and the food aspect of the overall quality of life can be improved.^{5,6} Furthermore, daily consumption of EY with scEW may contribute to earlier tolerance to egg.^{7,8} Nevertheless, the challenge foods used in egg yolk OFC have the disadvantage of a variable amount of egg white⁵ because egg yolk is separated manually from the whole egg.⁹ This disadvantage is overcomed by performing an OFC with 1/25 of a heated whole egg (low-dose egg) as egg juice, a product with a stable protein dose that varies only by 10%.^{10,11} Almost 80% of children with egg allergies can safely consume low-dose egg.¹¹ In vitro data of enzymelinked immunosorbent assay (ELISA) showed that low-dose egg juice has antigenicity (265.8 mg) similar to that of pumpkin cake, containing EY with scEW (213.2 mg).¹¹ Nevertheless, whether children who tolerate low-dose egg OFC can safely consume EY with scEW is unknown. This study aimed to examine the safety of EY with scEW consumption after negative results for low-dose egg OFC.

2 | METHODS

2.1 | Study design

As a part of a multicenter prospective study, we collected children's data for stepwise OFC, starting from low-dose egg OFC (250 mg egg protein, equivalent to 1/25 of a heated whole egg; UMIN000013026; Supinfo S1, Figure S1, Table S1). The study was undertaken at Sagamihara National Hospital as a part of a multicenter study between 2017 and 2018, as previously described.¹¹

2.2 | Eligibility criteria

Among children aged <18 years with a history of immediate reaction to eggs, children who passed the low-dose egg OFC participated in this study (Figure 1). Children with missing laboratory data or clinical information were excluded. Children who showed obvious or uncertain symptoms during OFC were also excluded.

2.3 | Materials

The challenge food was egg juice, which included 1 g of a cooked egg product and 39 mL of apple juice (Table S1). We provided the children's guardians with a recipe for egg yolk pumpkin cake (Table S1). Egg yolk

Key Message

We can safely recommend children with egg allergies to consume heated egg yolk slightly contaminated with egg white after negative results for 1/25 of a heated whole egg oral food challenge.

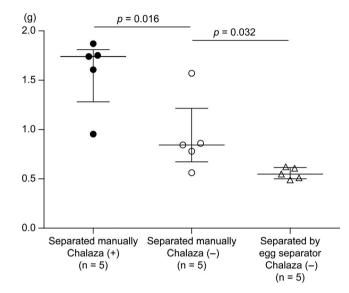


FIGURE 1 The amount of egg white contaminating the separated egg yolk. Egg yolk was separated manually with chalaza (n = 5), without chalaza (n = 5), and with an egg separator (n = 5) from one whole egg (approximately 50 g). The amount of egg white was 0.5-1.9 g (equivalent to 62.5-237.5 mg egg white protein)

pumpkin cakes were cooked by the guardians. We examined the protein doses of the challenge foods in advance (Table S1). Experimentally, the amount of egg white separated from whole egg was measured with and without chalaza or egg separator at Beppu University.

2.4 | Protocol

We advised children and their guardians to consume EY with scEW at home, starting with 1/8 of an egg yolk pumpkin cake and gradually increasing to 1/4, 1/2, and one egg yolk (home dosing). If ingestion of egg yolk provoked obvious symptoms, we advised guardians to stop home dosing. If ingestion of egg yolk provoked mild or uncertain symptoms, we advised them to confirm the reproducibility of symptoms by repeating the consumption of the same dose.¹² Guardians were required to record symptoms, if any, on a chart.

2.5 | Outcomes

The primary outcome of this study was the proportion of symptoms provoked by home dosing after a negative result for low-dose egg OFC. The secondary outcomes were the details of provoked symptoms at home (presence of skin, respiratory, gastrointestinal, neurologic, or cardiovascular symptoms) and treatments used for provoked symptoms.

2.6 | Sample size

We hypothesized that the expected proportion of reaction during home dosing is 0.9% and that the width of the confidence interval is 2.7%, based on a previous retrospective study.⁵ The whole sample size was calculated as 188.

2.7 | Statistical analysis

The Mann-Whitney *U* test was used for the analyses of continuous variables. The incidence of events was analyzed by the chi-squared test or Fisher's exact test as appropriate. A *p*-value <.05 was considered statistically significant. Continuous data were expressed as medians, and incidence of events was expressed as proportion. All analyses were performed using SPSS software (version 24.0 SPSS Inc).

2.8 | Ethical considerations

This study adhered to the principles of the Declaration of Helsinki. This study was approved by the Ethics Committee of Sagamihara National Hospital (Approval number: 2016-2-18). Written consent was obtained from the guardians of all children. Further details of the methods are shown in the Online Repository Text.

TABLE 1 Background characteristics of the participants

Background	(n = 276)
Sex (male)	188 (68%)
Age (y)	1.2 (0.9-2.2)
History of anaphylaxis in response to eggs	22 (8%)
Other food allergy	130 (47%)
Atopic dermatitis, current	156 (57%)
Bronchial asthma, current	14 (5%)
Allergic rhinitis, current	7 (3%)
Egg white sIgE (kU _A /L)	11.7 (5.4-26.5)
Egg yolk sIgE (kU _A /L)	1.8 (0.7-4.0)
Ovomucoid sIgE (kU _A /L)	5.3 (0.8-17.3)
Total IgE (IU/mL)	104 (46.3-367)

Note: Data are expressed as n (%) or median values, with 25% to 75% interquartile ranges provided in parentheses.

Data of egg yolk slgE levels were missing in 88 children.

Atopic dermatitis was well controlled in this study population. Abbreviation: slgE, specific immunoglobulin E.

3 | RESULTS

3.1 | Study enrollment

Among 495 children with egg allergies who previously reacted to eggs, 75 children were excluded due to missing laboratory data or clinical information (Figure 1). The children who showed obvious symptoms (n = 89) and uncertain symptoms (n = 65) were excluded. We followed 276 children who passed the low-dose egg OFC (Table 1).

3.2 | Study population

The median age of children was 1.2 years. One hundred and eightyeight (68%) of the children were male. Twenty-two children (8%) had history of anaphylaxis in response to eggs. The median egg whitespecific immunoglobulin E (IgE) level was $11.7 \text{ kU}_{\Lambda}/\text{L}$.

3.3 | Measurement of egg white

Experimentally, the amount of egg white separated from whole egg was measured with (n = 5) and without chalaza (n = 5), or without chalaza using egg separator (n = 5). The amount of egg white separated from the whole egg varied from 0.5 to 1.9 g (equivalent to 62.5-237.5 mg egg white protein; Figure 1). Removal of chalaza reduced the median amount of residual egg white significantly from 1.7 to 0.8 g (p = .016). Additionally, the use of egg separator reduced the amount of egg white significantly from 0.8 to 0.5 g (p = .032).

3.4 | Outcomes

Following home dosing, six children (2.2%) experienced mild symptoms (Figure 2). There were no significant differences in background between the six children who reacted and the 270 asymptomatic children (p = .218; Table 2).

Among the six children, five children were finally confirmed to continue the consumption of EY with scEW within 1 month after OFC, and mild skin symptoms were reproduced in one (0.4%) child who continued to avoid egg completely (Table 3). Immediate skin symptoms after ingestion were the most common for the five children who continued consumption, and none of the children experienced chronic symptoms. No children needed any treatment for the symptoms observed at home.

4 | DISCUSSION

Our study confirmed that most children with egg allergies can safely consume EY with scEW at home after negative results for low-dose

egg OFC. This safety data will help to improve their quality of life with regard to daily egg consumption.

A previous report showed that only 0.9% of children who passed egg yolk OFC reacted to EY with scEW at home dosing of egg yolk.⁵ Similarly, in our study, only six children (2.2%) reacted to home dosing and only one child (0.4%) continued to avoid egg completely. Although a significant difference was not observed, children who had symptoms at home showed higher ovomucoid levels (14.9 kU_a/L) than those without symptoms (5.2 kU_a/L).

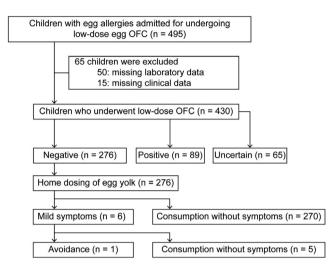


FIGURE 2 Patient enrollment. Low-dose oral food challenge (OFC) was administered. Among 495 children with egg allergies who previously reacted to eggs, 75 were excluded due to missing laboratory data or clinical information. The children who showed obvious symptoms (n = 89) and uncertain symptoms (n = 65) were excluded. We followed 276 children with negative results for lowdose egg OFC who had previously reacted to eggs

Therefore, we should pay attention to children with high ovomucoid slgE levels with regard to consumption of EY with scEW at home. Based on in vitro data, the antigenicities of low-dose egg juice and egg yolk-containing pumpkin cake are similar.¹¹ This study is the first to confirm that clinical reproducibility is also similar between these two products.

Although mild symptoms might occur, moderate-to-severe symptoms were not seen. Furthermore, most children who showed mild symptoms could eventually consume EY with scEW. This result is compatible with that of a previous report that showed that around 80% of children with mild uncertain symptoms can ultimately consume causative foods.¹² Therefore, we can safely recommend that children who passed the low-dose egg OFC consume EY with scEW. Although children with egg allergies are often sensitized to both egg yolk and egg white, and the reactivities to egg yolk and egg white have heterogeneous patterns, most children react to egg white.¹⁰ Although the egg yolk OFC is safe and useful,¹³ our study also confirmed that the amount of contaminating egg white in egg yolk OFC varies occasionally. Low-dose OFC overcomes the disadvantage of egg yolk OFC because the protein dose of low-dose egg juice OFC varies only by 10%. Most children with egg allergies can consume low-dose egg¹¹ and therefore improve their guality of life by safe consumption of low-dose egg product.¹⁴ Moreover, our study confirmed that most children could consume EY with scEW after low-dose egg OFC. Therefore, our findings suggest that the low-dose egg juice OFC can replace egg yolk OFC.

This study has several limitations. First, this study recruited only children who had previously reacted to eggs. Children sensitized to eggs may react less than those in this study. Second, in this study, no severe symptoms were reported. Severe symptoms may be provoked

No symptoms with home Mild symptoms with p-Background dosing (n = 270)home dosing (n = 6)value Sex (male) 184 (68%) 4 (67%) >.999 Age (y) 1.2 (0.9-2.3) 2.0 (1.4-3.3) .432 History of anaphylaxis in 21 (8%) 1 (17%) .395 response to eggs 125 (46%) 5 (83%) .103 Other food allergy Atopic dermatitis, current 152 (56%) 4 (67%) .700 Bronchial asthma, current 14 (5%) 0 (0%) >.999 Allergic rhinitis, current 7 (3%) 0 (0%) >.999 20.3 (12.6-91.6) Egg white sIgE (kU_{Δ}/L) 11.6 (5.3-26.7) .409 Egg yolk slgE (kU_{Λ}/L) 1.8 (0.7-4.1) 0.9 (0.1-0.9) .310 Ovomucoid sIgE (kU_{A}/L) 5.2 (0.8-17) 14.9 (1.9-99.4) .218 Total IgE (IU/mL) 104 (45.4-368) 196.9 (61.3-1998.3) .148

Note: Data are expressed as n (%) or median values, with 25% to 75% interquartile ranges provided in parentheses.

Data of egg yolk slgE levels were missing in 88 children.

Atopic dermatitis was well controlled in this study population.

Abbreviation: slgE, specific immunoglobulin E.

TABLE 2Differences in thebackground characteristics of theparticipants

IABLE 3		of symptoms ir	Detail of symptoms induced by home dosing					
Case	Age (y)	Sex	History of anaphylaxis to eggs	Egg white sIgE (kU _A /L)	Ovomucoid slgE (kU _A /L)	Avoidance of egg yolk 1 month after OFC	Dose of home consumption	Details of symptoms and treatment
1	1.6	Female	(-)	18.2	24.1	(+)	One egg yolk (pumpkin cake)	Mild skin symptom, vomiting, and cough/no treatment
							One egg yolk (pumpkin cake)	Mild skin symptom on the back 10 h after ingestion/ no treatment
2	0.9	Male	(-)	22.4	2.18	(-)	1/2 egg yolk (pumpkin cake)	Mild skin (lip)/no treatment
ო	2.0	Female	(+)	16.4	5.7	(-)	One egg yolk (pumpkin cake)	Mild skin symptom (lip)/no treatment
							One egg yolk (pumpkin cake)	Mild skin symptom (lip) Left eye swelling/no treatment
4	2.0	Male	(-)	25.1	26.5	(-)	1/8 egg yolk (pumpkin cake)	Mild skin symptom on the trunk/no treatment
							1/4 egg yolk (pumpkin cake)	Mild skin symptom on the trunk/no treatment
							1/4 egg yolk (pumpkin cake)	Mild skin symptom on the trunk/no treatment
							1/2 egg yolk (pumpkin cake)	Mild skin symptom on the trunk/no treatment
5	2.8	Male	(-)	1.06	1.12	(-)	One egg yolk (pumpkin cake)	Mild diarrhea/no treatment
9	4.9	Male	(-)	291	318	(-)	One egg yolk (hamburger steak)	Oral discomfort/no treatment
							1/8 egg yolk (pumpkin cake)	Mild skin symptoms (lip)/no treatment
Abbreviatio	1s: OFC, (oral food challe	Abbreviations: OFC, oral food challenge; slgE, specific immunoglobulin E	bulin E.				

TABLE 3 Detail of symptoms induced by home dosing

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in a study with a larger sample size. Unequal group sizes of children showing reactions and asymptomatic children could also be a potential limitation. Therefore, other studies with larger sample size may be required. Third, none of the cases reacted to heated whole egg at home. To confirm the reproducibility of negative OFC results, a further prospective study should evaluate the same heated whole egg powder. Finally, this study was not a double-blind placebo-controlled food challenge (DBPCFC). None of the enrolled children showed any symptoms during the OFC at the hospital. Therefore, open OFC may not have affected our result.

In conclusion, among children with egg allergies who passed the low-dose egg OFC, a few children may experience mild symptoms after home dosing, but most of them can ultimately consume EY with scEW. Therefore, we can safely recommend that children can consume EY with scEW after passing the low-dose egg OFC. To confirm the safety of this approach, we are now starting a further nationwide multicenter larger sample-size study including children sensitized to eggs, supported by the Japanese Society of Pediatric Allergy and Clinical Immunology.

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CONFLICT OF INTEREST

Motohiro Ebisawa serves on the clinical medical advisory board of DBV Technologies. Sato Sakura and Motohiro Ebisawa have received speaker honoraria from Mylan EPD. All other authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Noriyuki Yanagida: Conceptualization (lead); Data curation (equal); Formal analysis (lead); Funding acquisition (lead); Investigation (equal); Methodology (equal); Project administration (equal); Resources (equal); Software (equal); Supervision (equal); Validation (equal); Visualization (equal); Writing-original draft (lead); Writingreview & editing (equal). Sakura Sato: Conceptualization (equal); Data curation (equal); Investigation (equal); Resources (equal); Supervision (equal); Writing-original draft (equal); Writing-review & editing (equal). Kyohei Takahashi: Data curation (equal); Formal analysis (equal); Investigation (equal); Resources (equal); Software (equal); Supervision (equal); Writing-original draft (equal); Writingreview & editing (equal). Tomoyuki Asaumi: Conceptualization (equal); Data curation (equal); Investigation (equal); Resources (equal); Supervision (equal); Writing-original draft (equal); Writingreview & editing (equal). Ken-ichi Nagakura: Conceptualization (equal); Data curation (equal); Investigation (equal); Resources (equal); Supervision (equal); Writing-original draft (equal); Writingreview & editing (equal). Kiyotake Ogura: Conceptualization

(equal); Data curation (equal); Investigation (equal); Resources (equal); Supervision (equal); Writing-original draft (equal); Writingreview & editing (equal). **Nobue Takamatsu:** Data curation (equal); Formal analysis (equal); Investigation (equal); Resources (equal); Validation (equal); Writing-original draft (equal); Writing-review & editing (equal). **Motohiro Ebisawa:** Conceptualization (equal); Data curation (equal); Investigation (equal); Resources (equal); Supervision (equal); Writing-original draft (equal); Writing-review & editing (equal).

DATA AVAILABILITY STATEMENT

On reasonable request, the datasets used to support the findings of this trial are available from the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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