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Could egg yolk be the first approach in oral challenges for egg allergy tolerance?

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Key words

Egg allergy; food allergy; oral food challenges; egg yolk; pediatric patients.

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Impact statement

This study demonstrates that boiled egg yolk can be safely consumed by most children with egg allergies, potentially improving dietary options and quality of life.

Summary

Background. *Hen's egg allergy is one of the most common pediatric food allergies, requiring accurate diagnosis and management strategies. Oral food challenges (OFCs) are critical in evaluating food allergies; however, limited research has focused on the outcomes of challenges involving egg yolks. This retrospective study aims to assess the outcomes and characteristics of pediatric patients who underwent oral challenges with boiled egg yolk.* ***Methods.*** *We evaluated patients diagnosed with egg allergy who underwent an OFC with egg yolk between 2019 and 2022.* ***Results.*** *The study included 123 patients with a median age of 12 months. The first presentation of symptoms occurred at a mean age of 6 months. Initial symptoms included eczema flare-ups (70%), urticaria (13.8%), and anaphylaxis (8.9%). The median age of the first egg yolk OFC was 12 months. For the first egg white OFC to assess the tolerance, the median age was 16 months. Of the 123 egg yolk OFCs, 115 (93.4%) patients were tolerant and consumed egg yolk at home. In the egg yolk-tolerant group, the mean duration of egg white tolerance was 4 months post-OFC; for non-tolerant patients, this extended to 11 months. The egg yolk non-tolerant group had higher egg white-specific IgE levels than the tolerant group (28 kU/L [IQR: 2.4–85.9] vs 4.2 kU/L [IQR: 0.9–8.8], p < 0.01).* ***Conclusions.*** *Though mild symptoms may occur, most children with egg allergies can safely consume boiled egg yolk. Consuming hen's egg yolk after a negative OFC could expand dietary options and improve quality of life.*

Introduction

Egg allergy is a common food allergy affecting 0.5% to 2.5% of young children (1). Notably, it has the highest prevalence in children with atopic dermatitis and is second only to milk allergy in overall prevalence (2-4). The diagnosis of egg allergy is typically based on clinical history, skin prick testing (SPT), specific IgE (sIgE) measurements, and especially oral food challenge (OFC), which is considered the gold standard for determining tolerance levels and guiding dietary recommendations (5). These diagnostic criteria have been critical in identifying allergic reactions to hen's egg proteins, particularly the egg white fraction.

Boiled egg yolk is commonly used in dining, salads, and meals and is often better tolerated than egg white (6-7). Previous studies on egg allergies have mainly focused on the whole egg or egg white, with limited research investigating the outcomes of challenges involving boiled egg yolk. Considering that consuming egg yolk may lead to earlier tolerance and that incorporating various egg products can improve the nutritional variety and quality of life for children, it is important to pay more attention to this subject (8, 9).

Accurate diagnosis and management of egg allergy are essential to minimize the risk of adverse reactions and improve the quality of life for affected individuals. This retrospective study aims to evaluate the outcomes and safety of oral food challenges with boiled egg yolk in patients who have experienced a recent allergic reaction to a hen's egg and have highly elevated skin tests and specific IgE values.

Materials and methods

Study participants

This retrospective study analyzed data from the charts of patients with hen's egg allergy who underwent OFC for boiled egg yolk at Dr. Sami Ulus Children's Hospital between 2019 and 2022. The study included children who had their first egg OFC between the ages of 6 and 72 months and had a history of allergic reaction to whole hen's egg and tested positive for sIgE or SPT with egg, as specified in food allergy guidelines (10). Patients whose first provocation involved egg white were excluded from further analysis. Additionally, participants who were lost to follow-up after the initial diagnostic OFC and those with missing data regarding prognosis were also excluded.

Diagnostic procedures

Patients diagnosed with an egg allergy underwent a boiled egg yolk OFC after a 6-month follow-up period. Before the yolk OFC, all foods containing egg protein were removed from the children's diet. Participants who did not pass the first yolk OFC underwent a second challenge with egg yolk after a repeated 6-month elimination period, following our clinic's procedure. Participants who successfully completed the egg yolk OFC were instructed to consume boiled egg yolk once daily at home. Subsequently, an OFC with boiled egg white was planned, with the timing varying depending on factors such as the patient's test results, accidental exposure at home, the severity of the initial reaction, and the family's readiness, and was performed after they consumed egg yolk at home without any issues. Participants who did not pass the initial egg white OFC underwent a subsequent egg white OFC at least 6 months later.

The levels of sIgE were assessed using the fluorescent enzyme immunoassay (FEIA) system (IMMULITE Siemens, Germany). The results obtained from the fluorometer were evaluated in kU/L by the IgE standard calibrator. A measurement was considered positive if it was ≥ 0.35 kU/L.

Allergen extracts (Lofarma, Italy) were used for SPTs, which were performed on either the volar surface of the forearm or the back. SPTs were performed on the back in younger children for practical reasons, as it provided a larger surface area for testing and reduced movement during the procedure. Each test included both negative and positive controls to ensure accuracy and reliability. The negative control used was a saline solution, while the positive control was histamine. The mean wheal diameter was calculated 15 minutes after the test by determining the mean value of the longest diameter and the diameter perpendicular to it. To prevent any potential interference with the test results, any drugs that could impact the test, such as antihistamines, were discontinued seven days before the test.

Oral Food Challenge Protocol

This study utilized a 10-minute-boiled egg yolk for the egg yolk OFC and a 10-minute-boiled whole egg for the egg white OFC. The procedures were performed openly under the supervision of the same physicians and nurses at Dr. Sami Ulus Children's Hospital. The challenge food was administered at 15-minute intervals, starting with 1/16 of the total amount and increasing to 1/8, 1/4, 1/2, and the rest of the whole egg yolk or white. The OFC was terminated when the child developed severe symptoms, such as generalized urticaria, continuous coughing, severe abdominal pain, or vomiting. If mild objective symptoms, such as localized urticaria or pruritus, appeared during the OFC, the participant was carefully monitored for any worsening of symptoms. If the mild objective symptoms subsided, the OFC continued. In the event of an adverse reaction, the necessary medication was administered according to anaphylaxis guidelines (11). Additionally, patients were monitored for delayed reactions at home. In cases where delayed symptoms, such as eczema flare-ups, occurred after a negative OFC, patients were re-evaluated in the clinic to ensure proper management and adjustments to their diet.

Data collection

The main objective of this study was to evaluate the incidence of reactions during egg yolk OFC and determine whether participants could safely include egg yolk in their diet until they developed tolerance to egg white. The study included secondary data on allergy-related symptoms observed during the OFC and follow-up details, such as the duration of egg white tolerance.

Statistical analysis and ethical considerations

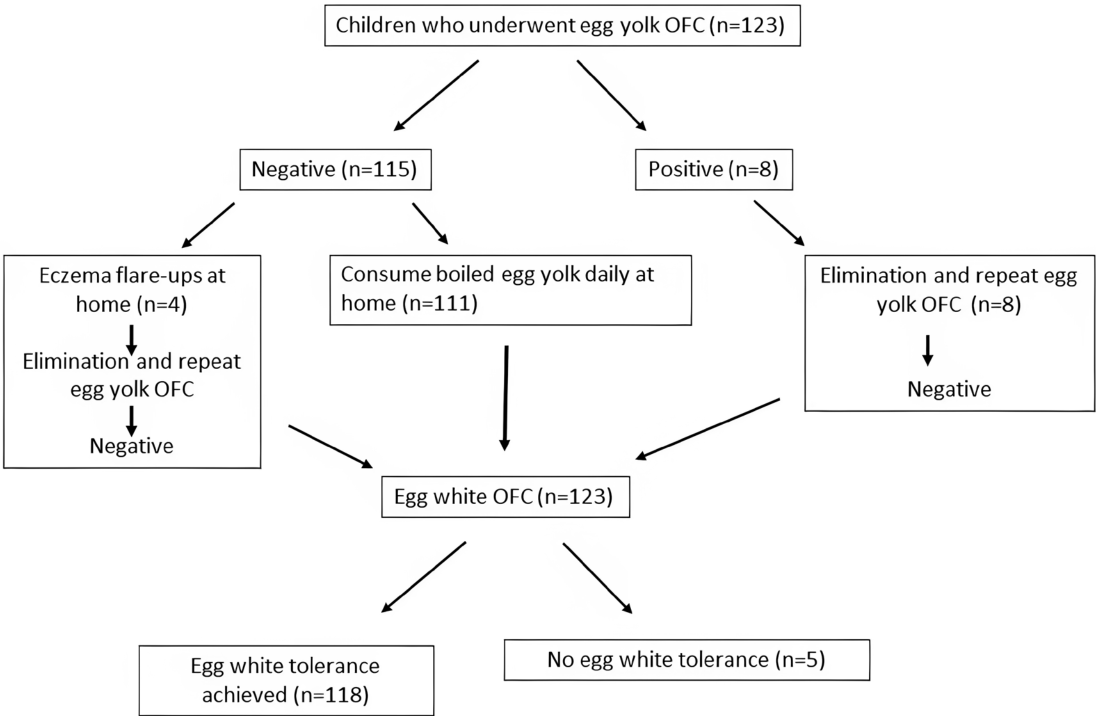
For statistical comparisons between the two groups, we used the Mann-Whitney U-test or Fisher's exact test. Differences in mean values were considered significant at $p < 0.05$. SPSS 26.0 (IBM Corporation, Armonk, NY, USA) was used for all statistical analyses. Categorical changes were compared with chi-square. The study was approved by the Clinical Research Ethics Committee of Ankara Training and Research Hospital (decision no: E-23-1233), and all procedures were conducted in accordance with ethical standards, ensuring privacy and confidentiality.

Results

Study participants

We analyzed the medical records of 210 patients who had undergone OFC for hen's egg allergy in our clinic. However, 30 patients

Figure 1 *- Flowchart of the enrolled patients.*



OFC: oral food challenge.

Table I *- Clinical characteristics of the study group who underwent an egg yolk OFC.*

Characteristics	All (n = 123)	EY-tolerant (n = 115)	EY-non-tolerant (n = 8)	P-value
Male gender, n (%)	80 (65)	76 (66)	4 (50)	0.22
Age, months	12 (9-16)	12 (9-16)	11 (8-15)	0.31
History of anaphylaxis, n (%)	11 (8.9)	9 (7.8)	2 (25)	0.063
Atopic dermatitis, n (%)	87 (70.7)	81 (70.4)	6 (75)	0.96
Asthma, n (%)	20 (16.2)	19 (16.5)	1 (12.5)	0.92
Allergic rhinitis, n (%)	9 (7.3)	7 (6)	2 (25)	**0.027**
Total IgE, IU/ml	25 (17-89)	25 (17-79)	53 (15-223)	0.47
Eosinophils, /µL	350 (220-550)	350 (220-550)	405 (270-508)	0.83
Basophils, /µL	50 (30-70)	45 (30-70)	50 (40-60)	0.99
Egg white sIgE, kUA/l	4.3 (1.1-13.1)	4.2 (0.9-8.8)	28 (2.4-85.9)	**<0.01**
Egg yolk sIgE, kUA/l	1.8 (0.2-6.8)	1.7 (0.2-4.2)	6.4 (1.4-12.6)	**<0.01**
Egg white SPT, mm wheal	5 (1-6.5)	5 (0-6.5)	5 (4.4-7.5)	0.20
Egg yolk SPT, mm wheal	0 (0-4)	0 (0-4)	3.5 (0-4.5)	0.10
Multiple FA, n (%)	71 (57.7)	66 (57.3)	5 (62.5)	0.69

EY: egg yolk; FA: food allergy; IgE: immunoglobulin E; sIgE: specific immunoglobulin E; SPT: skin prick test. Data are expressed as median (interquartile range) unless otherwise noted.

who were already tolerating egg yolk when they presented to our clinic were excluded from the study as they underwent OFC with egg white only. Furthermore, 57 patients (egg yolk tolerant: n = 55; egg yolk reactive: n = 2) were excluded from the study as they lacked follow-up information after undergoing OFC with egg yolk, making it unclear whether they developed tolerance to egg white. Therefore, the final study cohort consisted of 123 patients (**figure 1**).

Clinical characteristics

The study population had a median age of 12 months, as shown in **table I**. Eleven patients (8.9%) had a history of anaphylaxis to hen's egg. Atopic dermatitis was the most common allergic condition (70.7%), followed by asthma (16.2%). All patients with atopic dermatitis in our study experienced eczema flare-ups specifically after consuming egg, and these flare-ups improved when eggs were removed from their diet, indicating an allergic reaction. Among children with egg allergies, 57.7% had multiple food allergies. There were no significant differences in age, gender ratio, history of egg anaphylaxis, or comorbidities between the OFC-positive and OFC-negative groups. The group that tested positive during the OFC had higher serum total IgE and sIgE levels related to egg white and egg yolk.

OFC outcomes and tolerance

Out of 123 egg yolk OFCs, 115 (93.4%) patients were found to be tolerant and consumed egg yolk at home. For patients who could tolerate egg yolk, the average duration of egg white tolerance was 4 months after the initial OFC. However, the period was extended to 11 months for those unable to tolerate egg yolk.

Symptoms and treatment during OFC

We analyzed induced symptoms and symptom severity during the OFC. Skin symptoms were the most frequently reported, while two patients required intramuscular adrenaline injections due to anaphylactic symptoms during the egg yolk OFC. Both patients had a history of anaphylaxis after consuming eggs. One patient experienced a diffuse urticarial rash and recurrent vomiting, while the other had a persistent cough, dyspnea, and vomiting. After repeat elimination, participants who failed the initial yolk OFC underwent a second yolk OFC. Participants who passed the OFC for egg yolk were advised to consume boiled egg yolk daily at home. They then underwent a boiled egg white OFC after consuming the egg yolk at home without any problems. None of the patients who were OFC-negative with egg yolk developed a type 1 allergic reaction at home. However, in four patients, even though the oral challenge test was negative, it was necessary to discontinue egg consumption at home due to eczema flare-ups. In these cases, a repeat OFC was performed in a hospital setting before reintroducing eggs into the diet.

Discussion and conclusions

Most patients tolerate egg yolk OFCs well, unlike whole egg OFCs. Compared to 6.5% positive OFCs in our study, Yanagida *et al.* (12) reported a higher rate of 17%, while Okada *et al.* (8) reported a positive rate of 9.1% for egg yolk. In our study group, SIgE-egg white was measured at 4.3 kUA/L, similar to the value reported by Okada *et al.* (6.6 kUA/L), which is lower than the results of Yanagida *et al.* (13 kUA/L). The positive rates of OFC were found to be directly proportional to the sIgE levels of the group undergoing OFC, as expected. Studies have shown differences in pre-challenge-specific IgE levels. However, cut-off values predicting pre-challenge positivity rates cannot be applied uniformly across all studies. This is because the decision for the challenge depends not only on laboratory tests but also on factors such as the severity of the patient's previous reactions, accidental exposure at home, and the willingness of the family to accept the challenge. These positivity rates were notably lower than those reported in studies investigating whole egg OFCs, which ranged between 23% and 42% (13-14). Our study highlights the favorable safety profile of egg OFCs, consistent with other studies. This is supported by lower positive rates compared to whole egg challenges reported in the literature.

However, it is important to address the potential impact of the 57 patients (31.6%) lost to follow-up. While the number of patients lost to follow-up may raise concerns, it is crucial to note that the majority of these patients were lost during the pandemic period, when families were often hesitant to visit hospitals due to safety concerns. Clinical observations suggest that patients who develop tolerance to foods at home rarely return for follow-up evaluations, whereas those with persistent symptoms are more likely to seek follow-up care. This pattern suggests that most of the patients lost to follow-up likely tolerated egg yolk at home without significant symptoms, which supports the validity and robustness of our findings. Additionally, a worst-case scenario analysis was conducted to assess the impact of the 57 patients lost to follow-up. In this analysis, we assumed that the 55 patients who tolerated egg yolk did not achieve egg white tolerance, while the 2 patients who were reactive to egg yolk did achieve egg white tolerance. Despite these conservative assumptions, the results remained statistically significant, confirming the robustness of our findings.

Only two patients (1.6%) had severe reactions during OFC requiring intramuscular epinephrine injection. This is consistent with the results of other studies of egg yolk OFC (12, 15). None of the patients who tolerated egg yolk during OFC in our study had severe reactions at home. Exceptionally, four patients had to discontinue egg consumption at home because of eczema flares, even though the oral challenge test was negative. These delayed reactions underscore the importance of monitoring patients not only during the OFC but also afterward, as some allergic responses may manifest later. This is consistent with previous studies evaluating the safety of home consumption of egg yolk after a negative OFC (12, 15). These findings support the safe introduction of egg yolks at home, with careful follow-up to manage any delayed reactions, ultimately improving patients' quality of life.

For patients who were able to tolerate egg yolk, the average duration of egg white tolerance was 4 months after the first OFC. However, for those who could not tolerate egg yolk, this period was extended to 11 months. This is similar to the report by Okada *et al.* that the median time between the first egg yolk OFC and the first egg white OFC was 3.7 months for egg yolk-tolerant participants and 18.0 months for egg yolk-reactive participants (8). These findings suggest that tolerance to egg yolk could potentially predict the course of egg allergy.

Our findings suggest that incorporating boiled egg yolk into the dietary regimen of children with egg allergies offers a unique and complementary approach to established methods like egg white laddering. While these methods are highly effective with minimal adverse events, the introduction of egg yolk provides additional dietary flexibility and may serve as an intermediary step towards egg white tolerance, potentially enhancing overall quality of life for affected children.

This study had several limitations. One limitation of our study is the absence of an egg white OFC before the first egg yolk OFC. It is possible that some children had already outgrown their egg allergies by the time of the first egg yolk OFC. Additionally, the OFCs were not double-blind or placebo-controlled. Another limitation of the study was the small number of participants in the egg yolk reactive group. Therefore, further studies with larger sample sizes may be necessary. Given that our study was conducted during the pandemic, concerns about patients seeking medical attention and physicians' reservations about unnecessary hospital visits may have led to deviations from strict adherence to testing protocols. It is important to note that these deviations were not intentional and may have impacted the accuracy of our results. Furthermore, specific IgE measurements for Gal d 1 and Gal d 2, the main molecular components of egg, were not performed due to resource limitations. We recognize that these tests could have provided deeper insight into tolerance prediction and suggest their inclusion in future studies.

Most pediatric patients with an allergy to heated hen's egg can safely consume heated egg yolk. Although some children with egg allergies may experience mild symptoms, most can eventually tolerate egg yolk. This can improve their quality of life by making egg yolk products available after a negative OFC. The findings of the study emphasize the significance of sequential OFCs, beginning with heated egg yolk, for the diagnosis and evaluation of tolerance. These insights can inform clinical practice and provide a safer approach for reintroducing eggs into the diets of children with egg allergies.

Fundings

None.

Contributions

ST: conceptualization, methodology, data curation, visualization, writing – original draft. SD: conceptualization, data curation, formal analysis. MO: data curation, methodology. SS, SO: supervision, writing – review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

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