Efficacy, safety, and parental anxiety in a randomized trial of two dietary instruction methods for children with suspected hen's egg allergy

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Abstract

Background: Little has been reported on how to introduce hen’s egg into the diet of children with suspected egg allergy. We compared the efficacy, safety, and parental anxiety of two different dietary instruction methods to introduce egg.

Methods: Eligible participants were children aged 1–4 years who were positive for egg white IgE, and ovomucoid IgE <3.5 kUA/L. Participants were either naive in egg consumption or had a history of an immediate, but non-anaphylactic, allergic reaction to egg. After a negative result of baseline 2 g boiled egg white oral food challenge (OFC), participants were randomly assigned to the step-up OFC testing (SOFT) or home incrementing group. The primary outcome was the proportion of participants who were able to ingest 20 g of boiled egg white 6 months after initiation. This study is registered with the University Hospital Medical Information Network clinical trial registry (UMIN000024192).

Results: Between September 2016 and August 2018, we randomly allocated 55 participants to the SOFT (n = 33 [60%]) and home incrementing (n = 22 [40%]) groups and analyzed 51 patients. Four patients were excluded because they were lost to follow-up. Thirty-one (96.9%) of 32 participants in the SOFT and 12 (63.2%) of 19 in the home incrementing group achieved the primary outcome (p = 0.003). No serious adverse reactions were observed in either group. Parental anxiety significantly improved during treatment in both groups.

Conclusions: The SOFT method was more effective than home incrementing as dietary instruction to introduce egg in children with suspected egg allergy.

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Introduction

Hen’s egg allergy is one of the most common food allergies in childhood. The estimated prevalence of egg allergy is approximately 2% in children younger than 5 years. Although the principal method of managing food allergy is eliminating the causative foods, physicians should be prudent in their practice not to excessively eliminate causative foods, especially in children with suspected food allergy.

Oral food challenges (OFCs) are important for the diagnosis of food allergy, as well as to determine the threshold level of minimal avoidance. Full challenge dose OFCs are generally recommended for the initial diagnosis of food allergy. However, full-dose OFC risks overdosing beyond the threshold level, which might cause severe symptoms, and allergists might choose not to perform them in clinic or office settings to ensure the patient’s safety. Instead, low-dose OFCs are being performed in those settings. The approach to the patient after a negative low-dose OFC result is highly individualized. Most often, patients are advised to start consuming the causative food at home in an amount not exceeding the challenged dose, and to return for a re-evaluation of the dose increment using stepwise OFC testing after a certain period of time. In some cases, OFCs with increased amounts are performed to determine the threshold before starting intake. On the other hand, some allergy specialists instruct patients to gradually...
increase the amount at home.\textsuperscript{10,11} Little has been reported on the efficacy and safety of dietary instruction methods using stepwise OFCs or the home incrementing method to introduce food in children with suspected food allergy.\textsuperscript{9}

Parents of children with food allergy are predisposed to have ongoing fears of an allergic reaction and the consistent vigilance necessary to prevent accidental allergen ingestion.\textsuperscript{12} A number of studies have found that food allergy in a child is related to increased anxiety in the parents.\textsuperscript{12,13} Both proven food allergy and a suspicion of food allergy are associated with high levels of anxiety.\textsuperscript{12} Although there is debate over whether the anxiety levels of parents who suspect food allergy change before or after clinic visits,\textsuperscript{12,15} several studies have demonstrated that undergoing OFC reduces parental anxiety.\textsuperscript{16,17} To the best of our knowledge, however, there has been no report on parental anxiety during and after dietary instruction for children with suspected food allergy.

In the present study, we compared the efficacy and safety of two different dietary instruction methods to introduce egg into the diet of children with suspected egg allergy. Furthermore, we aimed to investigate whether differences in the instruction methods affect changes in parent’s anxiety during the treatment. To our knowledge, this is the first study conducted to confirm the efficacy and safety of the stepwise single-dose OFC method and the home incrementing method in children with suspected food allergy.

Methods

Study design and participants

In this randomized controlled trial, we recruited participants from Aichi Children’s Health and Medical Center in Japan. Participants were eligible for enrollment if they were 1–4 years of age and positive for egg white-specific IgE (sIgE) and ovomucoid sIgE <3.5 kUA/L. Blood tests were performed within 3 months before the enrollment. Participants were either naïve in egg consumption or had a history of an immediate allergic reaction to egg. Exclusion criteria were a history of anaphylactic reaction to egg, eating more than 2 g of boiled egg white at enrollment, a blood test performed before 1 year of age, complications of inadequately controlled atopic dermatitis or asthma, or complications of any severe disease. We obtained written informed consent from the parents of the participants at enrollment. The study was approved by the institutional review board of the Aichi Children’s Health and Medical Center (201641) and was conducted in accordance with the principles of the Declaration of Helsinki. This study is registered in the University Hospital Medical Information Network Clinical Trials Registry (UMIN 000024192).

Study protocols

Study visits were scheduled for visit 1 (enrollment OFC), visit 2, 3, and 4 (every 5–8 weeks after visit 1), and the final visit (4–6 weeks after visit 4). First, we performed an OFC using 2 g of egg white boiled for 20 min. Considering the outpatient setting, 2 g of boiled egg white was set as the initial amount that was considered safe to be consumed by participants with ovomucoid sIgE <3.5 kUA/L.\textsuperscript{18–20} After a negative OFC result, participants were randomly assigned to the step-up oral food challenge test (SOFT) or home incrementing groups on the basis of a computer-generated random number table (Fig. 1, Table 1). Participants in both groups were instructed to start ingesting 2 g of boiled egg white once a day at least four times per week.

Participants in the SOFT group underwent a single-dose stepwise OFC with 5, 10, and 20 g egg white (visits 2, 3, and 4, respectively), and continued ingesting the challenged dose if they passed the OFCs with no symptoms or mild symptoms. At the final visit, participants were asked whether they were able to ingest 20 g at home without symptoms. When allergic symptoms were provoked with the instructed ingestion, the dose was sustained or reduced according to symptom severity (see the safety outcomes). Detailed study protocols are provided in the Supplementary Materials.

Participants in the home incrementing group increased the dose approximately 20% at home every week when they successfully ingested the instructed dose. To be more precise, the dose was increased by 0.5 g per week between 2 and 5 g, 1 g per week between 5 and 10 g, and 2 g per week between 10 and 20 g. When the frequency of ingestion was fewer than four times per week, the participants continued the same dose without an increase. When allergic symptoms were provoked, the dose was reduced according to symptom severity. The participants in the home incrementing group visited an outpatient unit of the hospital every 5–8 weeks for follow-up examinations (visits 2, 3, and 4) and for the final visit.

All OFCs were open-labeled and conducted in accordance with the 2017 Japanese guideline for Food Allergy at the outpatient unit of the hospital.\textsuperscript{5} The participants’ parents prepared the egg white used for OFC and daily ingestion. Participants were instructed to avoid ingestion under some conditions, such as fever, asthma attack, or acute gastroenteritis. In addition, the participants were instructed to call the allergist of Aichi Children’s Health and Medical Center at any time in an emergency, or during office hours for nonemergency consultations regarding this study.

Outcomes

The primary outcome was the proportion of participants who were able to ingest 20 g of boiled egg white without symptoms on five consecutive occasions at the final visit. Secondary outcomes were maximum ingested amount of boiled egg white at the final
visit, and serum egg white and ovomucoid sIgE concentration as measured at the enrollment and final visit. Other secondary analyses included safety measurements, such as proportion of participants with adverse reactions or important medical events during the study period, changes in the parental anxiety scores, and skin condition (SCORing Atopic Dermatitis [SCORAD] and skin moisture meter) (Supplementary Materials, Supplementary Fig. 1).21

Safety outcomes

Adverse reactions, medications, and emergency hospital visits were recorded daily by parents in a diary and were assessed at every visit by study physicians. Adverse reactions were categorized as mild symptoms (e.g., perioral redness, hives, or itch; oral or pharyngeal discomfort; sneezing; and runny nose), moderate symptoms (e.g., local redness or hives; eye edema; laryngeal discomfort; mild transient coughing; mild nausea or abdominal pain; and loss of activity), and severe symptoms (e.g., multiple hives; intermittent coughing; difficulty in breathing; cyanosis; vomiting; diarrhea; strong abdominal pain; excitement or agitation; paleness; and cold extremities). These definitions are approximately equivalent to the following Sampson’s severity categories: mild symptoms, grade 1; moderate symptoms, grade 1 or 2; severe symptoms, grade 2 or 3.22 As judged by the study physician, adverse reactions were defined as related to the ingestion if symptoms occurred within 2 h after ingestion.

Immunological investigation

We measured total IgE and sIgE titers for egg white and ovomucoid (ImmunoCAP assay system, Thermo Fisher Scientific, Uppsala, Sweden), according to the manufacturer’s protocol. The examination was conducted within the 3 months before the first 2 g OFC and at the final visit. Egg white and ovomucoid sIgE titers less than 0.34 kUA/L and greater than 100 kUA/L were set to 0.34 kUA/L and 100 kUA/L, respectively.

Evaluation of parental anxiety

The validated Japanese translation of the State-Trait Anxiety Inventory (STAI) questionnaire was used to assess the parents’ anxiety.23,24 The STAI is a 4-point Likert-type scale with two parts measuring transient anxiety levels (state anxiety, STAI-S) and the individual’s stable trait (trait anxiety, STAI-T). The state anxiety represents how individuals feel at that time (e.g., “I feel nervous” or “I am worried”), whereas the trait anxiety indicates general feelings (e.g., “I generally worry too much over things that don’t really matter” or “I lack self-confidence”). The STAI comprises 20 questions in each part, and the scores range between 20 and 80, with higher scores indicating higher anxiety levels. The patients’ parents completed the STAI questionnaire prior to the first 2 g OFC in both groups, and prior to 5, 10, and 20 g OFCs in the SOFT group, or before the first ingestions of 5, 10, and 20 g at home in the home incrementing group. The same parent who completed the STAI at 2 g OFC in both groups, and prior to 5, 10, and 20 g OFCs in the SOFT group, or before the first ingestions of 5, 10, and 20 g at home in the home incrementing group. The same parent who completed the STAI at 2 g OFC completed all the subsequent questionnaires. STAI scores are commonly classified as “no or low anxiety” (20–37), “moderate anxiety” (38–44), and “high anxiety” (45–80).25

Statistical analysis

We estimated the proportion of the primary outcome successes of the home incrementing group to be 40% on the basis of our previous data,20 and that of the SOFT group to be 70% based on our pilot study (data not shown). Assuming an α risk = 0.05 and a β risk = 0.2 in a two-sided test, we estimated that 50 participants per group were needed. We also planned to finish enrollment at the end of August 2018 (an enrollment period of 2 years) even if there were fewer participants than in the planned sample size, considering advances in clinical practice.

All analyses were performed both on the intention-to-treat and the per-protocol sets. The intention-to-treat population included all participants who underwent randomization except for those who never ingested egg white after allocation, or who were lost to follow-up. The per-protocol set included participants who satisfied the inclusion criteria, attended all the study visits within the designed schedule, and adequately adhered to the dose increment rules. Worst-case imputation analyses were performed as a sensitivity analysis, in which participants lost to follow-up in the SOFT group were considered not to achieve the primary outcome and the participants lost to follow-up in the home incrementing group were considered to achieve the primary outcome.

For the analyses of secondary outcomes, differences in continuous variables between groups were assessed using the Mann-Whitney U test or the Wilcoxon rank-sum test, whereas differences in categorical data were examined using Fisher’s exact test. All analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria, version 3.5.1).26 For all analyses, a two-sided probability value p < 0.05 was considered to indicate statistical significance.

Results

Study population

Figure 2 shows the flow chart of the study participants. From September 2016 to August 2018, 55 participants (33 in the SOFT group and 22 in the home incrementing group) were enrolled in the study. Of these, 4 participants did not complete the study because they were lost to follow-up (1 in the SOFT group and 3 in the home incrementing group); 51 participants were evaluated for the primary and secondary outcomes and were included in the intention-to-treat analysis. Moreover, 5 participants discontinued the study due to maternal pregnancy (1 in the SOFT group), adverse reaction (1 in the home incrementing group), and nonadherence to study protocol (3 in the home incrementing group); 46 participants (31 in the SOFT group and 15 in the home incrementing group) were ultimately evaluated for the per-protocol analysis.
The baseline characteristics were well balanced between the groups (Table 2). The median (interquartile range, IQR) ages in months were 17.5 (14–23) in the SOFT group and 17 (15–23) in the home incrementing group. There were no significant differences in age, sex, or clinical features, including complication of atopic dermatitis, baseline SCORAD score, water content of the skin, history of immediate reaction to egg, or immunological parameters.

### Efficacy

The proportion of participants who were able to ingest 20 g of boiled egg white without symptoms 5 consecutive times at the final visit was 31 (96.9%) of 32 participants in the SOFT group and 12 (63.2%) of 19 in the home incrementing group (p = 0.003) in the intention-to-treat analysis (Table 3). The results in the per-protocol population were similar to those observed in the intention-to-treat population (p = 0.010) (Table 3). For the worst-case imputation analysis, 31 (93.9%) of 33 participants in the SOFT group and 15 (68.2%) of 22 in the home incrementing group achieved the primary outcome (p = 0.016) (Table 3). In the analysis of participants with no history of immediate reactions to egg white, we found significant difference in the primary outcome (p = 0.034, intention-to-treat population) (Supplementary Table 1). Results of the secondary clinical efficacy outcome are provided in Supplementary Table 2.

### Safety

One patient in the home incrementing group had a severe adverse reaction (multiple hives) with the first ingestion of 2 g egg white at home. This patient repeated the 2 g egg white OFC 2 weeks after the adverse event, which again resulted in multiple hives, and the patient discontinued the study (Fig. 2). All other adverse reactions were mild or moderate in intensity, and there was no medication used for symptoms or emergency hospital visits during the study period (Table 4).

A significantly higher proportion of ingestions associated with adverse reactions occurred in the home incrementing group than in the SOFT group (26 [0.83%] in the SOFT group and 49 [4.04%] in the home incrementing group, p < 0.001), mainly due to a significantly higher number of mild symptoms (21 [0.67%] in the SOFT group and 45 [3.71%] in the home incrementing group, p < 0.001) (Table 4). There was no significant difference in the number of moderate symptoms between the two groups (5 [0.16%] in the SOFT group and 4 [0.33%] in the home incrementing group, p = 0.27). The ingestion rate, calculated by the total number of ingestions between visits divided by the number of days between study visits, was significantly higher in the SOFT group (median 0.51 [IQR 0.46–0.59]) in the SOFT and 0.51 [IQR 0.46–0.59] in the home incrementing group, p = 0.007 (Table 4). Detailed profiles of dosing reactions expressed per participant are shown in Table 5. Adverse reactions were observed more frequently with the stepwise OFC doses than with the home doses in the SOFT group (4 [4.21%] of 95 ingestions with the OFC doses and 22 [0.56%] of 3029 ingestions with the home doses, p < 0.001) (Table 5). Adverse reactions in the home incrementing group were evenly observed between the increment doses and the maintenance doses (Supplementary Table 3).

### Immunologic parameters

There were no significant differences between the SOFT and home incrementing groups in terms of the baseline levels of total IgE.
IgE, egg white sIgE, or ovomucoid sIgE (Table 2). Comparing these immunologic parameters within each group before and after the study intervention, a significant reduction in egg white sIgE was observed in both study groups ($p = 0.001$ for the SOFT group and $p = 0.005$ for the home incrementing group by Wilcoxon rank-sum tests), whereas no significant changes in ovomucoid sIgE were observed in either group ($p = 0.38$ for the SOFT group and $p = 0.082$ for the home incrementing group by Wilcoxon rank-sum tests) (Table 2).

### Parental anxiety

Data were partially unmeasured in six participants (two in the SOFT and four in the home incrementing group), and answers from the mother and father were mixed in two participants in the SOFT group. As a result, STAI scores were analyzed from 28 of 32 parents in the SOFT and 15 of 19 in the home incrementing group, and all analyzed questionnaires were completed by the mothers. Before the start of 2 g OFC, baseline STAI scores did not differ between the SOFT and home incrementing group in both the STAI-S and STAI-T domains (Fig. 3). The STAI-S scores before 5 g OFC in the SOFT group were significantly lower compared with those at baseline ($p = 0.001$), and remained lower through 10 and 20 g OFC ($p = 0.006$ and $p < 0.001$, respectively) (Fig. 3A). The STAI-S scores before the first ingestion of 5 g in the home incrementing group were not significantly lower compared with baseline ($p = 0.09$), whereas the STAI-S scores before the 10- and 20-g ingestions were significantly lower than those at baseline ($p = 0.012$ and $p = 0.019$, respectively) (Fig. 3A). The STAI-T scores at each time point were not significantly different compared with the baseline in both groups (Fig. 3B).

### Discussion

In the present study, we compared the efficacy, safety, and parental anxiety of two different dietary instruction methods to introduce egg into the diets of children with suspected egg allergy. At the final visit (approximately 6 months after initiation), the stepwise OFC testing method, compared with home incrementing, resulted in a significantly higher proportion of participants who were able to ingest 20 g boiled egg white without symptoms. Safety was high and parental anxiety significantly decreased in both groups.

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**Table 5**

<table>
<thead>
<tr>
<th>Ingestion type type</th>
<th>No. of doses</th>
<th>Any symptom</th>
<th>Mild symptoms</th>
<th>Moderate symptoms</th>
<th>Severe symptoms</th>
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<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
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<tr>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Home dose (2 g)</td>
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<td>10</td>
<td>1.19</td>
<td>9</td>
<td>1.07</td>
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<tr>
<td>Home dose (5 g)</td>
<td>834</td>
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<td>0.84</td>
<td>6</td>
<td>0.72</td>
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<tr>
<td>Home dose (10 g)</td>
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<td>1</td>
<td>0.13</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Home dose (20 g)</td>
<td>564</td>
<td>4</td>
<td>0.71</td>
<td>4</td>
<td>0.71</td>
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<tr>
<td>Subtotal</td>
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<td>22</td>
<td>0.73</td>
<td>19</td>
<td>0.63</td>
</tr>
<tr>
<td>OFC dose (5 g)</td>
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<td>1</td>
<td>3.13</td>
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<tr>
<td>OFC dose (10 g)</td>
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<td>0</td>
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<td>0</td>
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<tr>
<td>OFC dose (20 g)</td>
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<td>6.25</td>
<td>1</td>
<td>3.13</td>
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<tr>
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<td><strong>Home increment group</strong></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Home dose (visit 1 to 2)</td>
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<td>16</td>
<td>4.27</td>
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<td>Home dose (visit 2 to 3)</td>
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<td>49</td>
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<td>45</td>
<td>3.71</td>
</tr>
</tbody>
</table>

1 participant had moderate symptoms and underwent repeated OFC.

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**Fig. 3.** Parental State-Trait Anxiety Inventory (STAI) anxiety scores. Change in (A) state anxiety (STAI-S) and (B) trait anxiety (STAI-T). *Represents a significant difference from the 2 g OFC ($p < 0.05$).
The proportion of primary outcome successes in the SOFT group was 96.9% in the intention-to-treat analysis, which was unexpectedly higher than our estimation. Although this proportion in the home incrementing group (63.2%) was higher than our estimation based on our previous report, the SOFT group achieved an extremely high success rate. The stepwise OFC testing method had been recommended in the 2017 Japanese guidelines for food allergy. In addition, Yanagida et al. had reported the usefulness and safety of stepwise and single-dose OFCs in patients with moderate to severe egg allergy. Our results provide new evidence that the stepwise OFC method is also efficacious in children with suspected egg allergy.

In terms of adherence, the ingestion rate was significantly higher in the SOFT group (Table 4). The less complicated instruction of continuing the same dose until the next stepwise OFC might have contributed to the higher adherence in the SOFT group and therefore the higher achievement rate of the primary outcome.

We found that parental self-reported anxiety improved significantly with dietary instructions for patients with suspected egg allergy, to the best of our knowledge, novel. Mothers of children with egg allergy had higher parental anxiety compared with mothers of children with no chronic illness. In line with this report, the initial parental STAI scores in our study were higher compared with the normative population. Significant improvements in parental anxiety from the baseline were observed at the time point of 10- and 20-g ingestions regardless of the study group. These improvements during and after dietary instruction are consistent with results from recent studies of patients with OIT. However, the comparison of two different dietary methods focusing on psychological aspects is one of the strengths of our study.

In our analyses of safety, adverse reactions in the SOFT group were more frequently observed with stepwise OFC doses than with home maintenance doses (Table 5). On the other hand, adverse reactions in the home incrementing group were evenly observed between increment doses and maintenance doses (Supplementary Table 3). Although higher prevalence of adverse reactions at OFC settings in the SOFT group might be due to a more precise evaluation of symptoms by physicians compared with parents, these differences should be noted. Another significant difference between the groups was the high proportion of mild symptoms in the home incrementing group. This difference might be explained by 2 participants reporting 27 and 10 times of perioral redness, respectively, out of 45 mild symptoms in the home incrementing group. For the other safety measures, we noted no significant differences between groups. There was no difference in the frequency or severity of adverse reactions irrespective of the presence or absence of a history of immediate reaction to egg white (data not shown). Although one participant in the home incrementing group withdrew from the study because of multiple hives after the first 2 g ingestion at home, this event was not related to the incrementing method. No medication usage, including adrenaline, and no emergency hospital visit was observed during the study period, implying the safety of both protocols.

Several studies have suggested that ovomucoid sIgE is more reliable than egg white sIgE in the diagnosis of a reaction to cooked egg. According to these studies, the positive predictive value for half a cooked egg white (approximately 20 g) in patients with ovomucoid sIgE less than 3.5 kUA/L would be 10%–30%. In line with this estimation, the pace of increment might work even faster than in our present study. However, use of a low-dose of 2 g egg white for the initial OFC might also have contributed to the safety of our protocols. Furthermore, although egg white sIgE levels were very high in some participants (>50 kUA/L; four in the SOFT group and three in the home incrementing group, intention-to-treat population, data not shown), the study protocols were conducted safely in the participants who met our inclusion and exclusion criteria.

There are a number of limitations in this study. First, the participants included children with egg sensitivity with no history of allergic reaction to egg. These participants might have passed the 20 g OFC at initiation and could have avoided unnecessary continuous consumption of eggs. The lack of a confirmed diagnosis before the intervention may be a major shortcoming of this study. However, physicians are examining such patients in the real world, despite the limited data regarding dietary instruction to these children published to date. Here, we proposed models of the procedure to introduce egg in patients with suspected egg allergy. Second, this study was a single-center design at a specialty hospital, and the results might not be representative of the majority of patients with egg allergy. Multicenter studies should be conducted in the future to confirm the efficacy and safety of dietary instructions to introduce egg in patients with suspected egg allergy. Third, this study was conducted in participants with relatively low ovomucoid-sIgE levels, and further study is needed to determine whether similar results can be obtained in patients with severe egg white allergy. Fourth, a difference in protocols between the groups might have affected the primary outcome. The duration between visits was 5–8 weeks in both groups; however, participants in the SOFT groups were allowed to proceed to the next stepwise OFC if they had more than 3 eligible weeks (a week with ingestions once a day for more than 4 days); whereas, participants in the home incrementing group needed at least 5 weeks to reach the same amount of the next stepwise OFC, considering the increase rate of 20% per week.

Our study was unable to recruit the planned number of participants by the end of the study period. However, there was an unexpectedly large group difference in the primary outcome by Fisher’s exact test analysis. In addition, the allocated number of participants in both groups was unbalanced, despite our randomization procedure using a computer-generated random number table. Since we used simple randomization, it was a possibility; however, this could have biased the result toward a larger difference between the groups.

In conclusion, the SOFT method was more effective than home incrementing as a dietary instruction to introduce egg in patients with suspected egg allergy. Our study provides clear evidence that both stepwise single-dose OFCs and home incrementing methods can be applied effectively and safely in children with ovomucoid sIgE lower than class 2. We hope this study will contribute to improving food allergy management in children with suspected egg allergy in specialty hospitals and clinics, as well as in general practitioner clinics.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.alit.2020.07.007.
Conflict of interest
The authors have no conflict of interest to declare.

Authors’ contributions
KSaK, KSsS, SS and IK conceived and designed the study. KK analyzed the data and wrote the manuscript. SS supervised KK’s work. KK, KSaK, TM, YT and SS recruited the participants and collected the data. All authors contributed to interpretation of the data. IK is the principal investigator of the study. All authors read and approved the final manuscript.

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