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Tolerance to cooked egg in infants with risk factors for egg allergy after early introduction of baked egg

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Abstract
Egg allergy (EA), along with cow's milk allergy (CMA) and atopic dermatitis (AD), is one of the most frequent allergies in children. Tolerance to food allergens seems to be related to the early and regular intake and the cooking method. The objective of this study is to prove that the introduction of baked eggs at 4-6 months of age and its daily maintenance for 6 months prevents EA. Controlled randomized clinical trial from February 2019 to November 2023 was done for all patients under 6 months of age, including those with CMA and/or AD without previous egg consumption. Skin prick test (SPT), specific immunoglobulin E (sIgE), basophil activation test (BAT), and oral food challenge (OFC) on baked eggs were performed at the beginning of the study (T0). Patients were classified into group A (nontolerant to baked egg) following an egg-free diet and group B (tolerant to baked egg). These were randomized into B1 who ate baked egg daily and B2 who avoided egg. Six months later, at time 1 (T1), an OFC to hard-boiled egg was performed. There were 27 patients in all. Those who ate baked egg daily for 6 months tolerated boiled eggs and only 47.4% of patients who followed an egg-free diet tolerated boiled eggs (*P*-value 0.012). All three tests—sIgE, SPT, and BAT—are considered good techniques to discriminate between tolerant versus not tolerant patients toward eggs. Patients under 6 months of age with CMA and/or AD who ate baked eggs daily for 6 months tolerated cooked eggs more frequently than patients who avoided eggs. Early introduction of baked eggs could prevent EA.

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Introduction

In the pediatric population (between birth and 18 years), egg allergy (EA), along with cow's milk allergy (CMA) and atopic dermatitis (AD), is one of the most frequent allergies.[1] Food allergy (FA), mainly EA, should be considered in infants with moderate or severe AD or CMA. Infants sensitized to eggs without previous consumption may react with the first intake,[1] where sensitization can occur during breastfeeding or damaged skin.[2]

The diagnosis of FA is performed after medical history is noted, SPT, sIgE, BAT, and OFC, which is still the gold standard to confirm the diagnosis.[3] As OFCs are risky, objective diagnostic criteria to identify patients most likely to pass them are of great interest. BAT is a relatively new diagnostic method, which aims to reduce in vivo testing, and appears to have promising results.[4]

EA has a good prognosis in most cases, even though up to 20% of children continue to be allergic into adulthood.[5] There are different therapeutic options for FA: food avoidance, oral immunotherapy (OIT), or treatment with biologics, but there is still a risk of accidental reaction to hidden food.

More scientific studies are in order to discover new treatments to reduce the risk and prevent serious food reactions.

Tolerance to food allergens seems to be driven by regular and early exposure to proteins during a critical window of immunologic development. Although the timing of this window is not clear, current evidence suggests that it could be between 4 and 6 months of life; delayed exposure may increase the risk of FA.[6-8]

Introduction to eggs in the children's diet is an ongoing discussion. Several investigations focus on a possible tolerance to baked egg in children who have nil tolerance to cooked and/or raw egg.[9-14]

The main objective of this study is to know if the introduction of baked egg at 4–6 months of age and its daily maintenance for 6 months could prevent EA in children along with CMA and/or AD. This study also aims to describe the clinical characteristics of patients with CMA/AD in relation to sensitization/allergy to egg as well as the immunological changes that occur in children under 6 months of age to 12 months who follow a regular egg ingestion for 6 months.

Methods

A controlled randomized clinical trial was conducted, including patients under 6 months of age, with CMA and/or AD without previous egg consumption, who visited the Paediatric Allergology and Clinical Immunology Department at Sant Joan de Déu Hospital, Barcelona, between February 2019 and November 2023. All patients provided written informed consent before inclusion. The study was approved by the hospital's Ethics and Research Committee with number PIC-121-19.

The ratios (sIgE/tIgE) were calculated after SPT, total IgE (tIgE), sIgE (to egg and its components—egg white, egg yolk, ovomucoid, and ovalbumin), and BAT to eggs were performed at the beginning of the study (T0) as well as baked egg OFC. SPT was performed using commercially available egg and component extracts (LETI Pharma, Spain). sIgE to egg and components were measured by ImmunoCAP system, Thermo Fischer Scientific, Uppsala, Sweden. At the beginning of this study, a recipe for baked egg sponge cake was given to families (annex 1) with the instruction that it should have a total weight of approximately 300 g containing 19.5 g of egg protein. Families baked the cake and brought it to perform the OFC. To calculate the grams of egg protein at each dose of OFC, the cake was weighed and the protein grams were calculated. During OFC, increasing doses of cake were administered to the patient. The protocol was different for egg-sensitized and non-egg-sensitized patients (annex 2).

A BAT with whole egg extract (Ovo-Des NM®) on heparinized whole blood to assess basophil activation by measuring CD63 expression by flow cytometry was performed following the manufacturer's procedure (Basostep®; Immunostep®). The final concentrations of allergen tested were 1, 0.5, 0.1, and 0.001 mg/mL, as reported earlier. A monoclonal anti-IgE antibody (SigmaAldrich) was used as positive control. To evaluate basal degranulation values, the stimulation buffer was used as a negative control. The staining reagent contained a mix of anti-CD63-FITC, CD203cPE/HLA-DR per CP/CD123 APC monoclonal antibodies. Briefly, flow cytometric analysis of the cells was performed using a flow cytometer (FACS canto II, BD bioscience) for acquisition and using DIVA software for analysis. Basophilic cells were selected out of the lymphocyte populations as CS123+/CD203c+/HLA-DR. At least 1000 basophils were assessed in each assay to consider it valid. Basophil activation in response to the allergen and positive controls was calculated as the percentage of the CD63+ cells within the total identified basophil cells minus the percentage of the CD63+ cells upon stimulation with stimulation buffe only (CD63 + net). A lack of stimulation when using the positive control (10% CD63 + basophils) was considered as a criterion for excluding the sample from the study.[15-17]

The patients were classified into two groups. Group A: patients who had no tolerance for baked eggs were advised to follow a diet without eggs, and group B: patients who tolerated baked eggs. Group B patients were randomized into two subgroups, group B1 who consumed baked eggs daily, and group B2, who avoided eggs for the next 6 months. Six months later, at time 1 (T1), an OFC to hard-boiled eggs (annex 3) was performed on all patients (Figure 1).

OFC to baked eggs and/or to hard-boiled eggs were considered positive if typical symptoms of IgE-mediated reaction appeared or after the worsening of AD (increase of at least 10 points on the "SCORAD" scale during the following 7 days.[18]

Parameters collected at inclusion were age, gender, history of EA and/or AD, and allergic comorbidities. SPT and sIgE values, BAT, and type of reaction at OFC at T0 and T1 were also recorded.

First, a descriptive analysis of the database was carried out. Frequency tables were generated for categorical variables and the corresponding descriptive statistics were calculated for numerical variables. Quartile-quartile curves were used to study the normality of these variables. The relationship between variables was studied by performing a bivariate analysis. For the relationship between two categorical variables, the Chi-squared test or

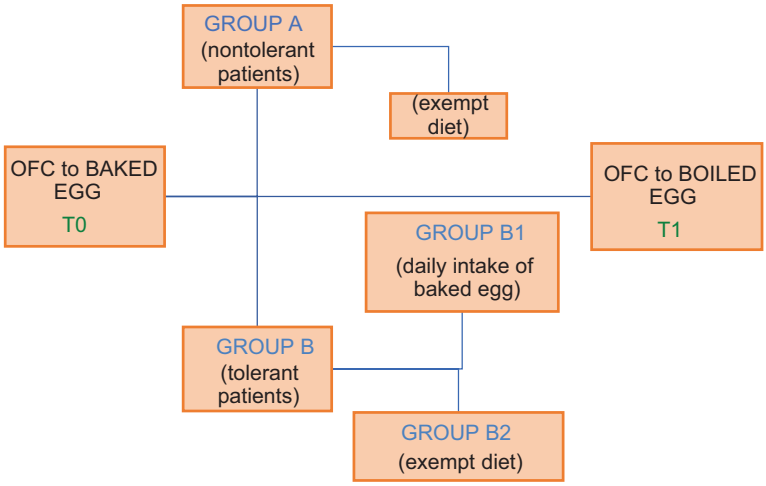

Figure 1 Distribution of patients in the study.

Fisher's exact test was used. For the relationship between a numerical variable and another categorical variable, parametric (T-student) or nonparametric (Mann-Whitney U test) comparison tests were used, depending on the distribution in the numerical variable. In cases where significant differences were detected in the mean comparison tests, receiver operating characteristic (ROC) curves were generated to study the possible cutoff points. Finally, repeated measures ANOVA test was used (performing logarithmic transformation in cases where it was convenient) to study the evolution of numerical variables between the two follow-up points and the differences in this evolution according to the diet assigned to each case.

Results

Of the 27 patients (< 6 months old, 74% male), 16 (59%) had CMA, 9 (33%) AD, and 2 (7.4%) had both conditions; 19 (70,3%) were sensitized to egg, and of these, 7 (36%) had a positive OFC to baked eggs (2 of them with an anaphylactic reaction); 20 patients who tolerated baked eggs were randomized in B-1 (8 patients) who ate baked eggs daily and B-2 (12 patients) who avoided eggs. Patients who ate baked egg daily for 6 months tolerated boiled eggs more frequently than patients who avoided eggs (*P*-value 0.012). In fact, all patients who ate baked eggs daily for 6 months tolerated boiled eggs at T1; however, only 47.4% patients who followed an egg-free diet tolerated boiled eggs at T1 OFC (Table 1).

Analyzing only patients from group B (tolerant to baked eggs in T0), the same result was observed (*P*-value 0.042) (Table 2).

There were no statistically significant differences in tolerance to baked eggs between patients with CMA, AD, or both.

Table 1 Comparison of total patients who ate baked egg daily versus those on an exempt diet in relation to boiled egg OFC at T1. Fisher's exact test.

Total Patients	Boiled egg OFC	
	Tolerant	Nontolerant
Daily intake of baked eggs	8 (100%)	0
Exempt diet	9 (47.4%)	10 (52.6%)

P-value. Fisher's exact test 0.012.

Table 2 Comparison of group B patients who ate baked eggs daily versus those on an exempt diet in relation to boiled egg OFC at T1. Fisher's exact test.

Group B Patients	Boiled egg OFC	
	Tolerant	Nontolerant
Daily intake of baked eggs	8 (100%)	0
Exempt diet	6 (50%)	6 (50%)

P-value. Fisher's exact test 0.042.

Diagnostic tests: Prediction of response to baked egg OFC at T0

Egg white, yolk, and ovalbumin sIgE were significantly higher in patients who could not tolerate baked eggs compared to those who did (*P*-value 0.018, 0.045, and 0.036, respectively). No differences were observed in the ratios (sIgE /tIgE) between the two groups.

All patients who could not tolerate baked eggs had a positive BAT to egg, whereas within patients who tolerated baked eggs, 42% had a negative BAT to eggs (*P*-value 0.062).

Diagnostic tests: Prediction of response to boiled egg OFC at T1

The same analysis was carried out at T1 in relation to boiled egg OFC. The values of egg white, yolk, ovalbumin, and ovomucoid sIgE were significantly higher in patients

who could not tolerate boiled eggs compared to those who were able to tolerate them (*P*-value 0.018, < 0.009, 0.05, and 0.05, respectively). All ratios were higher in patients that could not tolerate boiled eggs compared to those who could tolerate them (*P*-value < 0.009, < 0.009, 0.009, and 0.018, respectively).

Ninety percent of patients who could not tolerate boiled eggs had a positive BAT to eggs, whereas 93% of the patients who tolerated boiled eggs had a negative BAT to eggs. A high agreement was observed between positive BAT and subsequent reaction in OFC as well as negative BAT and negative OFC to boiled eggs (*P*-value < 0.001).

Immunological changes from T0 to T1

Analyzing whether the ratios evolved differently between patients who consumed baked eggs daily versus those on an exempt diet, statistically significant differences were observed in the egg white/tIgE ratio (*P*-value 0.018). In patients with daily intake of baked eggs, the egg white ratio decreased more compared to patients not consuming egg. Figure 2 shows how the egg-free diet group keep egg white ratio values between T0 and T1 while the daily intake group significantly decreases it (Figure 2).

ROC curves to determine sIgE cutoff points

At T0, there are good areas under the curve (AUCs) with egg white, yolk, and ovalbumin-sIgE, with values of 0.9, 0.8, and 0.8, respectively (Table 3). This allowed us to determine optimal cutoff points with high sensitivity and specificity. At T1, there is a good AUC in all sIgE values: 0.8, 0.9, 0.8, and 0.8, respectively (Table 3).

Discussion

In this study, a total of 27 patients with CMA and/or AD younger than 6 months of age were included. there were more male children with EA than female; EA is more common in male children.[32] Seventy percent of the patients were sensitized to eggs, and of these, 36% had a reaction at the baked egg OFC.

A study by Álvaro et al. showed that in their sample of patients with CMA and/or AD, 69% were sensitized to eggs,[1] and of these sensitized patients, 71.3% reacted to boiled or raw egg OFC. In this study, the percentage of patients sensitized to eggs is similar, but EA on challenge showed a lower percentage. This could be explained because Álvaro et al. performed boiled or raw egg OFC, while in this study OFC was

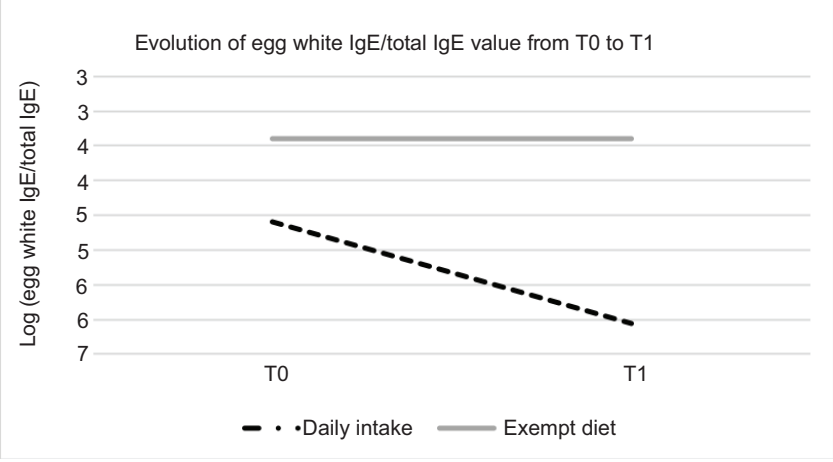

Figure 2 Evolution of egg white IgE/tIgE ratio from TO to T1. Comparison of patients with daily intake of baked eggs to patients who avoided eggs.

Table 3 Specific IgE ROC-AUC curves at T0.

	AUC	Optimal cutoff point	Sensitivity	Specificity
Egg white T0	0.907	0.63	100	75
Yolk T0	0.864	0.3	71.4	90
Ovalbumin T0	0.871	1.44	85.7	90
Ovomucoid T0	0.65			
Egg white T1	0.869	0.4	100	76.5
Egg yolk T1	0.922	0.65	100	88.2
Ovalbumin T1	0.810	1.16	66.7	88.2
Ovomucoid T1	0.827	0.4	77.8	88.2

performed with baked eggs, which, as suggested by this work and other published studies, seems to be less allergenic.[9-14]

It is also shown that CMA and/or AD is highly related to EA, not finding significant differences between AD and CMA patients in relation to this condition.

Most patients in our sample tolerated baked eggs at T0, but of the nontolerant, two (28.5%) elicited an anaphylactic reaction. This result is similar to other studies that have reported cases of anaphylaxis in relation to OFC to baked eggs.[14-19] OFC should be performed in a hospital with the necessary facilities to treat severe reactions. The two patients that suffered an anaphylactic reaction in our study did not share clinical characteristics, so we could not relate this reaction to clinical features.

In this study, patients who ate baked eggs for 6 months tolerated hard-boiled eggs, and even omelet, in a higher percentage than those who avoided eggs (*P*-value 0.012). In fact, all patients who ate baked eggs daily tolerated cooked eggs 6 months later, regardless of whether the patients were previously sensitized to eggs or not. This result, in line with previous studies, suggests that in patients at risk of FA, early and regular introduction[20-25] to baked food[9-14] could prevent the development of FA.

The current gold standard for FA diagnosis is OFC. As OFCs are risky, diagnostic criteria to identify patients most likely to pass them are of great interest.[1,3,26,27] Currently, multiple studies have proposed the ratio of sIgE/tIgE as a predictive value of the OFC outcome in comparison to sIgE. Our study suggests that at T0, sIgE is more useful to predict OFC outcomes. Nevertheless, at T1, the ratio is more useful than sIgE. Previous literature reports different results in relation to sIgE versus the ratio of sIgE/tIgE.[28-30] Currently, in clinical practice, our recommendation is to perform both values, ratio, and sIgE.

In relation to ROC curves, at T0, sIgE to egg white, yolk, and ovalbumin were found to be good predictors to identify patients who react at baked egg OFC. At T1, all sIgE were good predictors to identify patients who reacted to boiled egg OFC. At T0, egg white sIgE has a cutoff point of 0.63 with a sensitivity of 100%. All patients with values below this cutoff did not react to baked egg OFC, which suggests that an egg white sIgE < 0.63 is safe. It would be interesting to perform new studies to confirm this result, with the aim of introducing baked eggs to these patients at home or at hospital, maybe with faster schedules. At T1, the cutoff point for egg white and yolk are 0.4 and 0.65 KUI/L, respectively, also showing a sensitivity of 100%.

In our sample, positive BAT to egg is highly suggestive of positive baked or cooked egg OFC and negative BAT is predictive of tolerance. This correlates with previous studies that suggests BAT as a new diagnostic tool to predict OFC outcome.[15-17] Clinical validation studies are required, but in the near future it may serve to predict OFC responses.

The evolution of tIgE and ratios (sIgE/tIgE) over time between T0 and T1 have been analyzed. tIgE in all patients was higher at T1 than at T0, which correlates with previous studies that described a tIgE increase in the first years of life.[31]

Of note, between T0 and T1, egg white/tIgE ratio decreased more in patients who ate baked eggs daily compared to those who avoided eggs. But patients who followed an egg-free diet kept the same values of egg white/tIgE ratio over time, from T0 to T1.

Taking into account that one of the results from our study is that patients with higher egg white/tIgE ratio react more at boiled egg OFC, it can be concluded that the daily intake of baked eggs helps to reduce the egg white/tIgE ratio, and therefore, increases boiled egg tolerance.

Conclusions

This study is a randomized clinical study, which aims to evaluate prevention strategies for FA. Currently, this is a topic of high interest with diverse scientific evidence and a high impact on clinical guidelines for infants' complementary feeding. Also, this study included all patients with CMA or AD who presented in a tertiary hospital. Furthermore, all allergy cases were confirmed with OFC.

1. In patients under six months of age with CMA and/or AD, the early introduction of baked eggs daily for 6 months prevents cooked EA.
2. CMA and/or AD are relevant to identify infants at risk of sensitization and/or allergy to eggs, and therefore, to be candidates for preventive strategies.
3. Baked egg OFC should be performed in a hospital with facilities to treat severe reaction.
4. There is a high agreement between BAT result and the OFC outcome. BAT is a diagnostic tool with a promising future in FA.
5. In patients who eat baked egg daily, egg white/tIgE ratio decreases significantly between T0 and T1, with a good correlation with boiled egg tolerance.

This study also has limitations, the main being the small sample size, which becomes more evident when patients are divided into multiple groups. The follow-up of these patients was long and complex, which lead to a high drop-out rate. Nevertheless, and despite these limitations, this study opens a door to EA prevention given the very positive results.

Key Message

FA is increasing. The usual approach of food introduction in infants until recently may have had an impact in the development of FA. New research in this area with an early introduction of foods can be the clue for preventing FA. Nevertheless, research which involved the introduction of raw or cooked eggs has had many adverse events; however, the introduction of baked foods (baked eggs in this case) can induce an immunomodulatory effect in the patient inducing tolerance of the specific food and minimizing the risk of allergic reactions. This work can have an impact in diminishing FA in our infants, toddlers, and later in our life without putting patients at risk of severe allergic reactions.

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Authors Contributions

All authors contributed equally to this work.

Conflicts of Interest

None.

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Supplementary

S1. Cake Recipe

Ingredients:

- 3 large eggs
- 100 g wheat flour
- 50 g sugar
- 1 big spoon olive oil (15 mL)
- 1 small spoon yeast (4 g)

Beat the egg whites and add the rest of the ingredients. Let it rest for 15 minutes. Bake for 20 minutes at 180°C in the oven.

S2. OFC to baked eggs (T0)

The cake will have a total weight of approximately 300 g and 19.5 g of egg protein (6.5 g of egg protein per egg).

During the OFC, increasing doses of the cake will be administered to the patient. The protocol will be different for sensitized and non-sensitized patients. Doses are administered every 30 minutes. After the last dose, the patient must remain 3 hours under observation.

OFC to sensitized patients:

- 0.1 g egg protein (1.5 g cake)
- 0.2 g egg protein (3 g cake)
- 0.4 g egg protein (6 g cake)
- 0.8 g egg protein (12 g cake)
- 1.5 g egg protein (23 g cake)
- 2 g egg protein (30 g cake)

OFC to non-sensitized patients:

- 0.2 g egg protein (3 g cake)
- 0.8 g egg protein (12 g cake)
- 2 g egg protein (30 g cake)

In all patients who tolerate baked cake, the daily dose at home will be 1.5 g egg protein (23 g cake).

S3. OFC to boiled egg (T1)

During the OFC, increasing doses of boiled eggs will be administered to the patient. Doses are administered every 30 minutes. After the last dose, the patient must remain 3 hours under observation.

OFC to boiled egg:

- 0.3 g boiled egg white
- 1 g boiled egg white
- 3 g boiled egg white
- 9.5 g boiled egg white
- 30 g boiled egg white
- One egg omelet