Dietary baked egg accelerates resolution of egg allergy in children

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Background: Baked egg is tolerated by a majority of egg-allergic children.
Objective: To characterize immunologic changes associated with ingestion of baked egg and evaluate the role that baked egg diets play in the development of tolerance to regular egg.
Methods: Egg-allergic subjects who tolerated baked egg challenge incorporated baked egg into their diet. Immunologic parameters were measured at follow-up visits. A comparison group strictly avoiding egg was used to evaluate the natural history of the development of tolerance.
Results: Of the 79 subjects in the intent-to-treat group followed for a median of 37.8 months, 89% now tolerate baked egg and 53% now tolerate regular egg. Of 23 initially baked egg–reactive subjects, 14 (61%) subsequently tolerated baked egg and 6 (26%) now tolerate regular egg. Within the initially baked egg–reactive group, subjects with persistent reactivity to baked egg had higher median baseline egg white (EW)-specific IgE levels (13.5 kU_A/L; $P = .04$) than those who subsequently tolerated baked egg (4.4 kU_A/L; $P = .04$) and regular egg (3.1 kU_A/L; $P = .05$). In subjects ingesting baked egg, EW-induced skin prick test wheal diameter and EW-, ovalbumin-, and ovomucoid-specific IgE levels decreased significantly, while ovalbumin- and ovomucoid-specific IgG_4 levels increased significantly. Subjects in the per-protocol group were 14.6 times more likely than subjects in the comparison group ($P < .0001$) to develop regular egg tolerance, and they developed tolerance earlier (median 50.0 vs 78.7 months; $P < .0001$).
Conclusion: Initiation of a baked egg diet accelerates the development of regular egg tolerance compared with strict avoidance. Higher serum EW-specific IgE level is associated with persistent baked and regular egg reactivity, while initial baked egg reactivity is not. (J Allergy Clin Immunol 2012;130:473-80.)

Key words: *Egg allergy, baked egg, heated egg, food allergy, egg tolerance, oral food challenge, egg oral immunotherapy*

Egg allergy affects an estimated 1.8% to 2% of children younger than 5 years.[1] A recent study from Australia reported 8.9% prevalence of challenge-proven allergy to uncooked egg in a large cohort of infants younger than 12 months.[2] While 80% of children eventually outgrow egg allergy, and most in the general population do so by school age, studies indicate that many children evaluated at referral centers are retaining egg allergy into their teenage years.[3-5] It appears that the longer the egg allergy persists, the less likely tolerance will develop.[4] Thus, it has become imperative to understand individualized prognosis of egg allergy and develop clinical management that will improve the quality of life of egg-allergic children and, ideally, promote earlier tolerance development.

Food processing alters protein structure and affects allergenicity. Previous studies indicated that some egg-allergic individuals tolerate baked egg.[6-9] Heating may decrease allergenicity by destroying conformational epitopes or blocking epitope access through interactions with the food matrix (eg, wheat flour), as seen in egg and milk.[10] Children with IgE antibodies predominantly against conformational ovomucoid (OVM) epitopes are more likely to have transient allergy as opposed to those with IgE antibodies against sequential epitopes not altered by heating.[11,12] Indeed, studies have shown that baked egg tolerance occurs prior to regular egg tolerance.[7,13]

In the clinical trials conducted at our center, 70% to 75% of egg- and milk-allergic children tolerated baked egg or milk, respectively.[14,15] In the above-mentioned population-based study conducted in Australia, 80.3% of the children with challenge-proven raw egg allergy tolerated a baked egg challenge.[2] We recently reported that inclusion of baked milk accelerates resolution of milk allergy.[16] In the initial phase of the baked egg study, we confirmed that baked egg is well tolerated and associated with decreasing egg white (EW)-induced skin prick test (SPT) wheal diameter and serum ovalbumin (OVA)-specific IgE level, and increasing serum OVA- and OVM-specific IgG_4 levels. These immunologic changes parallel those seen in the natural resolution of egg allergy and associated with food oral immunotherapy (OIT).[5,17-19] In this article, we present long-term immunologic changes and clinical outcomes of egg-allergic children who included baked egg in their diet. We evaluate predictors of baked and regular egg tolerance and assess

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Abbreviations used
EoE: Eosinophilic esophagitis
EW: Egg white
OFC: Oral food challenge
OIT: Oral immunotherapy
OVA: Ovalbumin
OVM: Ovomucoid
SPT: Skin prick test

whether the ingestion of baked egg reduces the time to the development of regular egg tolerance.

METHODS

Participants

Subjects between 0.5 and 25 years of age with documented IgE-mediated egg allergy were recruited from the pediatric allergy clinics at the Mount Sinai Medical Center in New York, NY. Documented IgE-mediated egg allergy was defined by a positive EW SPT result and/or detectable (≥0.35 kU_A/L) serum EW-specific IgE level, and a recent history (within the past 6 months) of a type I hypersensitivity reaction to egg or a positive physician-supervised oral food challenge (OFC) to egg; or, if no history of recent reaction, a serum EW-specific IgE level greater than 2 kU_A/L in children younger than 2 years or greater than 7 kU_A/L in children older than 2 years.[3,20] Subjects were excluded from the study if they had a negative SPT result and undetectable serum EW-specific IgE level, a recent (within the past 6 months) type I hypersensitivity reaction to baked egg, already tolerated and were ingesting baked egg, or a history of eosinophilic esophagitis (EoE), unstable asthma, or pregnancy. The study was approved by the Mount Sinai Institutional Review Board, and informed consent was obtained before enrollment.

Design

Tolerance to baked egg (muffin and waffle) was determined by OFC as previously described.[14] Subjects tolerant to baked egg were challenged with regular egg. Regular egg-tolerant subjects were instructed to incorporate all forms of egg into their diet and were encouraged to do so at least twice a week. Baked egg–tolerant subjects were instructed to incorporate baked egg products into their diets. Baked egg–reactive subjects were instructed to strictly avoid all forms of egg.

Active group

Subjects in the active group were categorized as baked egg–tolerant or baked egg–reactive. Subjects tolerant to baked egg were advised to consume 1 to 3 servings of baked egg per day and avoid regular egg as previously described.[14] Subjects ingesting baked egg were reevaluated every 3 to 12 months, and after 6 months or more were offered challenges to regular egg. Subjects reactive to baked egg were offered repeat challenges to baked egg after 12 months or more.

Immunologic evaluation

SPTs were performed as previously described.[21] A serum sample was collected at each visit to measure EW-, OVA-, and OVM-specific IgE and OVA- and OVM-specific IgG_4 levels by using UniCAP (Phadia, Uppsala, Sweden).

Oral food challenges

OFCs were performed openly under physician supervision in the Mount Sinai Clinical Research Center. During baked egg challenges, a muffin and a waffle each containing one third of an egg (2.2 g of egg protein) were administered.[14] (See Fig E1 for baked-egg muffin recipe in this article's Online Repository at www.jacionline.org.) Baked egg–tolerant subjects were challenged to regular egg if their test results were less than the 95% positive predictive values for a positive OFC result: EW-specific IgE level less than 2 kU_A/L in children younger than 2 years or less than 7 kU_A/L in children older than 2 years, or an EW SPT wheal diameter less than 8 mm.[3,20,22,23] For regular egg challenges, scrambled egg or French toast was administered (1 egg or 6.5 g of egg protein) as per routine protocol.[24]

Comparison group

We retrospectively identified comparison egg-allergic subjects who were age-, sex-, and IgE-matched with active subjects at the time of enrollment. The same inclusion and exclusions criteria were used, and none of the control subjects had tolerated or were ingesting baked egg at the time of enrollment. Subjects in the comparison group continued strict egg avoidance (current standard of care).[25] If they added baked egg to their diet, it was due to accidental exposures. They were challenged to regular egg as per their allergist's recommendation.

Statistics

All statistical analyses were performed with SAS Version 9.2 (SAS Institute, Inc, Cary, NC). A Wilcoxon rank-sum test was used to compare medians of continuous measures, whereas the χ^2 test (and the Fisher exact test when the expected cell count was <5) was used to compare distributions of categorical measures between various subject groups. A Wilcoxon signed-rank test was used to compare medians of continuous measures at different time points. Logistic regression models with nominal (using a generalized logit link function) and ordinal (using a cumulative logit link function) outcomes were used to estimate odds ratios, corresponding 95% CIs, and *P* values with adjustment for sex, age, and initial IgE values. Probabilities of regular egg tolerance were estimated with the Kaplan-Meier product limit method, with comparison among groups evaluated with the log-rank test statistic. The Cox proportional hazards model was used to estimate hazard ratios, corresponding 95% CIs, and *P* values with adjustment for sex, age, and initial IgE values. All statistical hypothesis testing was performed at the .05 level of significance.

Intent-to-treat versus per-protocol analysis

The intent-to-treat analysis includes 79 subjects who underwent the initial baked egg challenge, were available for follow-up, and either reacted to baked egg or regular egg, or tolerated baked egg but had immunologic indications of greater than 95% risk of reaction to regular egg.[3,20] The per-protocol analysis includes those subjects (n = 70) who were, or eventually became, tolerant to baked egg over the course of the study and underwent treatment by adding baked egg to their diet (Fig 1).

RESULTS

Baseline clinical characteristics

Between June 2004 and September 2007, 117 subjects were enrolled in the study. Detailed baseline characteristics at the time of enrollment were previously described.[14] Briefly, 79 subjects (71% males) were included in the intent-to-treat group, with a median age of 5.8 years (range, 1.6-15.8) and a median initial serum EW-specific IgE level of 2.5 (range, 0.2-101), and were followed for a median of 37.8 months (range, 7.6-69.7). At baseline challenge, 56 (71%) subjects in the intent-to-treat group were baked egg–tolerant and 23 (29%) were baked egg–reactive (Fig 1). The remaining 38 of the 117 subjects initially enrolled and challenged were not included in the analysis because they tolerated regular egg at baseline challenge (n = 24), refused to ingest the entire baked egg serving resulting in an inconclusive baseline challenge (n = 3), developed subsequent non–IgE-mediated intolerance to egg (n = 1), were lost to follow-up after the baseline baked egg challenge (n = 3), or passed the baseline baked egg challenge but regular