

ORIGINAL ARTICLE

Food Allergy & Anaphylaxis

Gal d 1-specific IgE predicts allergy to heated egg in Finnish children

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Abstract

Background: Allergen-specific IgE levels can be useful in predicting outcomes of oral food challenges, but optimal cutoff levels vary in different populations. The aim was to determine cutoff values for egg white- and Gal d 1-, Gal d 2-, Gal d 3-, and Gal d 4-specific IgE (sIgE) predicting positive oral heated egg challenges in 185 Finnish children and adolescents.

Methods: A total of 185 egg-sensitized patients (age: 1-19 years, median: 6.3, mean: 7.0 years) with suspected egg allergy underwent double-blind, placebo-controlled (n = 78), or open (n = 107) oral food challenges with heated egg white. Specific IgE levels to egg white, Gal d 1 (ovomucoid), Gal d 2 (ovalbumin), Gal d 3 (conalbumin), and Gal d 4 (lysozyme) were measured by ImmunoCAP and compared with challenge outcomes.

Results: Of the 185 challenges, 124 (67%) were positive. Gal d 1 sIgE levels were significantly higher in the challenge-positive (median 13.5 kU/L, mean 33.2 kU/L) than in the challenge-negative group (median 0.2 kU/L, mean 1.2 kU/L), $P < 0.0001$. The diagnostic capacity of sIgE to egg white and Gal d 2, 3, and 4 was clearly weaker. In ROC analysis, the AUC for egg white was 0.86, Gal d 2 0.84, Gal d 3 0.79, and Gal d 4 0.77. Sensitization to Gal d 1 with a cutoff of value of >3.7 kU/L predicted a positive challenge with a specificity of 95% and sensitivity of 78%. The likelihood ratio was 15.9. In ROC analysis, the area under the curve was 0.94 (95% CI, 0.91-0.97). With a cutoff value of >14 kU/L, all challenges were positive, and with a cutoff of <0.9 kU/L, 95% of the challenges were negative. In the children aged 1-5 years (n = 88), the cutoff for Gal d 1 was >3.8 kU/L, and in the children above 6 years of age (n = 97), it was >3.5 kU/L.

Conclusion: Gal d 1-specific IgE is useful in distinguishing egg-sensitized patients with clinically reactive egg allergy from those tolerant of heated egg. The optimal cutoff point in a Finnish population of 185 children and adolescents was 3.7 kU/L with no significant difference between the younger and older age groups.

KEYWORDS

allergen component, egg allergy, Gal d 1, IgE, ovomucoid

1 | INTRODUCTION

Hen's egg allergy, with an estimated prevalence of 0.5–2.5% in the Western World, is one of the most common food allergies in infants and young children.^{1,2} Early childhood egg allergy is associated with aeroallergen sensitization and asthma in later life, and children with atopic dermatitis are frequently sensitized to hen's egg.^{3,4}

Egg allergy is transient and outgrown by school age in most children.^{5,6} These children typically have mild symptoms and low specific IgE levels at baseline. Approximately 70% of egg-allergic children tolerate egg in the heated form,^{7,8} and regular consumption of baked egg products seems to accelerate the development of tolerance to unheated egg as well.⁹ In about 20%, egg allergy persists until teenage years.¹⁰ Persisting allergy is associated with a more severe clinical course, high specific IgE levels, and allergy to both raw and heated egg.⁵

Allergens characterized in egg white include Gal d 1 (ovomucoid), Gal d 2 (ovalbumin), Gal d 3 (conalbumin), and Gal d 4 (lysozyme) with protein contents of 11%, 54%, 12%, and 3%, respectively. These four allergens constitute up to 80% of the total egg white protein content.¹¹ Gal d 1 is the most dominant egg allergen; it remains soluble even after extensive heating and is stable against enzymatic digestion. Sensitization to Gal d 1 predicts clinical reactivity to both raw and heated egg and is considered a risk factor for persistent egg allergy.^{6,12,13} Gal d 2, 3, and 4, on the other hand, are unstable proteins readily degraded by heating and enzymatic digestion, which reduces their allergenicity.¹¹ Patients sensitized to sequential epitopes of Gal d 1 are more likely to have persistent allergy compared with those sensitized to conformational epitopes in the unstable egg allergens Gal d 2–4.¹² Sensitization to Gal d 2 in the absence of IgE to Gal d 1 predicts reactivity to raw egg only.¹⁴ The clinical importance of Gal d 3 and 4 remains unclear.

Allergen-specific IgE levels can be useful in predicting outcomes of oral food challenges. A number of studies have determined food-specific IgE levels resulting in a more than 95% probability for a positive challenge outcome, known as 95% predictive decision points.¹⁵ These cutoff levels, however, vary in different populations. Geographical and cultural factors, age, and dietary habits influence sensitization profiles, whereas referral bases and challenge procedures influence the challenge outcome. Therefore, optimal cutoff levels need to be determined for each population and each allergen separately. The aim of this study was to determine cutoff levels for allergenic components in egg white predicting positive challenges to heated egg in Finnish children and adolescents.

2 | METHODS

2.1 | Patients

The study included 185 consecutive children and adolescents, aged 1–19 years, referred to the Department of Allergology, Helsinki University Central Hospital, Finland, for evaluation of egg allergy.

Their median age was 6.3 years, and 54% of them were male. Eighty-eight (48%) were aged 1–5 years (mean: 2.4, median: 1.9 years), and 97 (52%) were 6 years or older (mean: 11.2, median: 10.6 years). All patients underwent open or double-blind, placebo-controlled food challenges (DBPCFC) with heated egg white. The participants were recruited between June 2013 and March 2017.

All patients were sensitized to egg white (egg white-specific IgE ≥ 0.35 kU/L or skin prick test ≥ 3 mm). We included both diagnostic baseline challenges in egg-sensitized children with suspected egg allergy and rechallenges in egg-allergic children, who were being evaluated for possible resolution of the allergy. We performed DBPCFC in 78 patients above 6 years of age, who were being considered for forthcoming egg oral immunotherapy and open challenges in 107 patients.

The Helsinki University Hospital of Children and Adolescents Ethics Committee approved the study, and each participant above 6 years of age as well as his/her guardian gave written informed consent.

2.2 | Oral challenges

We performed open egg challenges with boiled egg white in increasing doses (35, 140, 350, and 750 mg protein) given at 30-minute intervals. The cumulative dose was 1225 mg corresponding to one-third of an egg white. We performed DBPCFC on two nonsuccessive days with spray-dried egg white powder (Dava Foods, Piispanristi, Finland) or placebo (soy powder) heated and masked in fried meatballs. The interval between the challenge doses (5, 50, 200, 500, and 1000 mg protein) was 30 minutes. The cumulative dose was 1775 mg corresponding to one half of an egg white.

The challenges were interpreted positive and dosing was stopped in line with the PRACTALL consensus criteria.¹⁶ We used a modified threshold-adjusted score to evaluate reaction severity: 1–5 indicated mild, 6–13 moderate, and 14–23 severe reactions.¹⁷ Symptoms were treated with antihistamine, and/or intramuscular epinephrine, and/or oral steroids.

2.3 | IgE measurements

Serum samples were collected from all participants. Serum IgE levels to egg white (f1), Gal d 1 (ovomucoid), Gal d 2 (ovalbumin), Gal d 3 (conalbumin), and Gal d 4 (lysozyme) were measured by ImmunoCAP (Thermo Fisher, Uppsala, Sweden).

2.4 | Statistics

For analysis of data, we used GraphPad Prism 6.05 for Windows (GraphPad Software Inc., La Jolla, CA, USA) and SPSS Inc. (Chicago, IL, USA) version 21 software. We used receiver operating characteristics (ROCs) to estimate cutoff levels, sensitivity, specificity, and likelihood ratios for specific IgE. Correlation between IgE levels, eliciting dose, and symptom score was analyzed using Spearman's rank correlation. Mann-Whitney *U* test was used to compare nonnormally

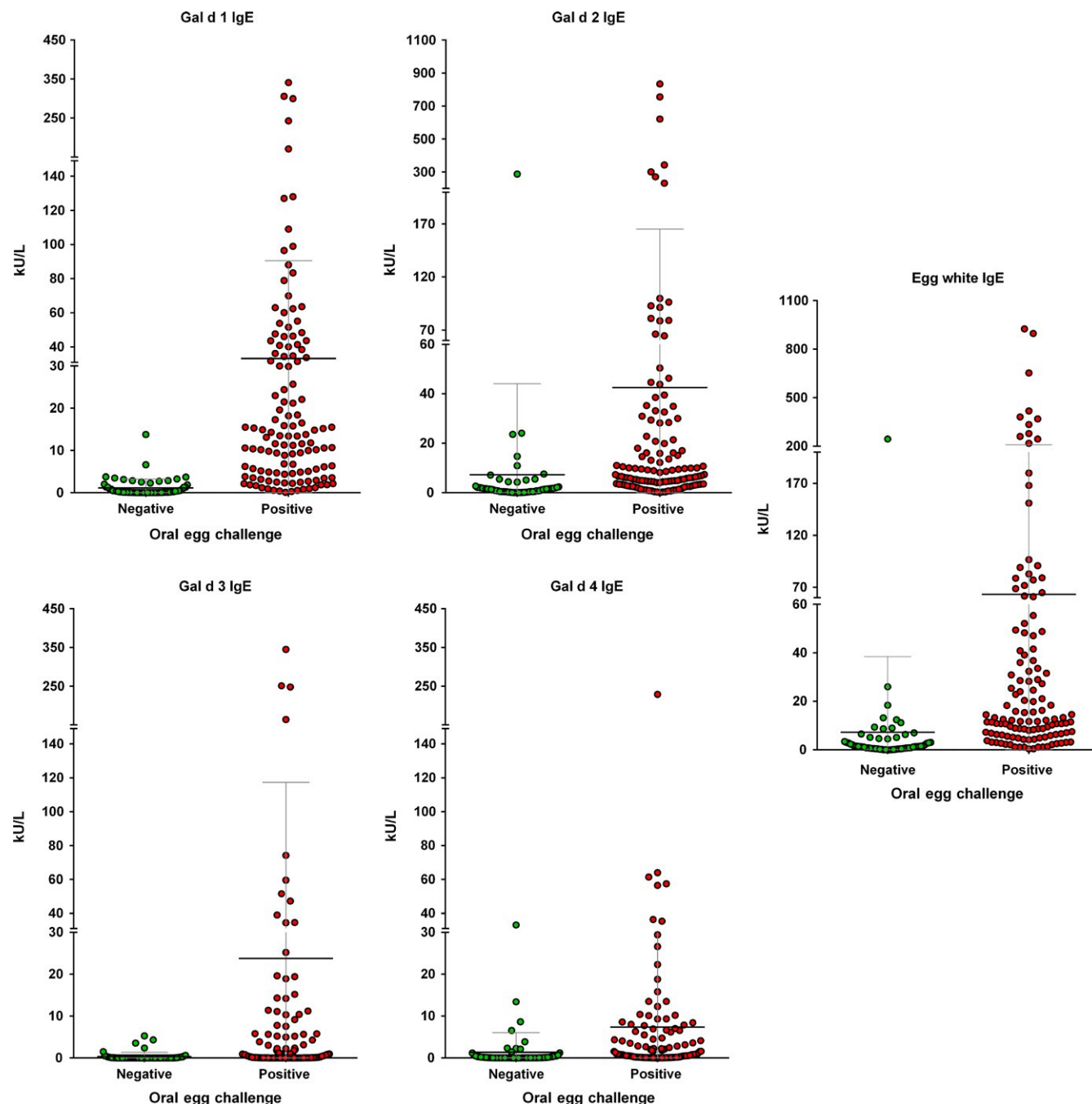


FIGURE 1 Gal d 1-4 and egg white specific IgE levels (kU/L) in 124 challenge-positive and 61 challenge-negative patients [Colour figure can be viewed at wileyonlinelibrary.com]

distributed data. A P -value of <0.05 was considered statistically significant.

3 | RESULTS

Of the 185 challenges, 124 (67%) were positive and 61 (33%) negative. Seventeen (14%) challenges were graded as mild, 77 (62%) moderate, and 30 (24%) severe. The median cumulative eliciting dose was 455 mg (5-1755 mg) of egg protein.

The most typical symptom, observed in 40% of the positive challenges, was nausea, prolonged (>40 minutes) abdominal pain, or vomiting, preceded by oral pruritus. Of the 124 positive challenges, 104 (84%) presented with gastrointestinal symptoms, 59 (48%) oral allergy syndrome, 51 (41%) skin symptoms, 26 (21%) respiratory symptoms, and 11 (9%) laryngeal symptoms (Table 1). Twenty-four patients were treated with adrenaline. Six of them experienced anaphylaxis, and 18 patients with severe reactions were given adrenaline proactively to prevent the development of severe anaphylaxis. Three patients with anaphylaxis received multiple adrenaline doses.

TABLE 1 Symptoms in 124 positive challenges

	n	%
Skin	51	41
Pruritus	16	13
Urticaria	30	24
Flushing	29	23
Upper or lower respiratory	26	21
Wheezing, coughing	15	12
Rhinitis	16	13
Conjunctivitis	16	13
Laryngeal edema, throat tightness	11	9
OAS	59	48
Gastrointestinal	104	84
Nausea	42	34
Prolonged (>40 min) or severe abdominal pain	84	68
Vomiting	29	23
Diarrhea	13	11
Anaphylaxis	6	5

Gal d 1 sIgE levels were significantly higher in the challenge-positive (median 13.5 kU/L, mean 33.2 kU/L, range 0.1-340.1 kU/L) than in the challenge-negative group (median 0.2 kU/L, mean 1.2 kU/L, range 0-13.8 kU/L), $P < 0.0001$ (Figure 1). Sensitization to Gal d 1 with a cutoff of value of >3.7 kU/L predicted a positive challenge with a specificity of 95% and sensitivity of 78% (Figure 2). The likelihood ratio was 15.9. In ROC analysis, the area under the curve (AUC) was 0.94 (95% CI, 0.91-0.97; Figure 2). With a cutoff value of >14 kU/L and sensitivity of 48%, all challenges were positive. The cutoff for a negative challenge outcome with 95% sensitivity and 69% specificity was <0.9 kU/L.

There were no significant differences in the 95% predictive decision points between the different age groups. In the children aged 1-5 years ($n = 88$), the cutoff for Gal d 1 was >3.8 kU/L, and in the children above 6 years of age ($n = 97$), it was >3.5 kU/L (Figure 2). There was, however, a tendency of lower Gal d 1 levels (median 9.3 kU/L, mean 16.8 kU/L, range: 0.3-88 kU/L, AUC 0.93) in the challenge-positive children under 3 years of age ($n = 32$). The cutoff of >3.7 kU/L gave a 94% specificity, a 75% sensitivity, and a likelihood ratio of 13.5 in this age group ($n = 68$). The median cumulative eliciting dose was, as well, lower in these children, being 184 mg compared with 525 mg ($P < 0.05$) in participants over 3 years of age ($n = 92$).

The diagnostic capacity of sIgE to egg white and Gal d 2, 3, and 4 was weaker. The IgE levels were significantly higher in the challenge-positive group than in the challenge-negative group for egg white, Gal d 2, and Gal 4, but not Gal d 3 (Figure 1). In ROC analysis, the

AUC for egg white was 0.87 (0.82-0.93), Gal d 2 0.84 (0.77-0.90), Gal d 3 0.79 (0.72-0.85), and Gal d 4 0.77 (0.69-0.85). The 95% predictive values gave low sensitivities (23%-42%) and likelihood ratios demonstrated in Figure 2.

Specific IgE levels did not associate with symptom severity scores, threshold doses, nor cumulative eliciting doses. Specific IgE to egg white correlated strongly with Gal d 2 ($r = 0.95$) and Gal d 1 ($r = 0.90$) and to a lesser extent with Gal d 3 ($r = 0.71$). IgE to Gal d 1 correlated with Gal d 2 ($r = 0.79$), but not with Gal d 3 or 4.

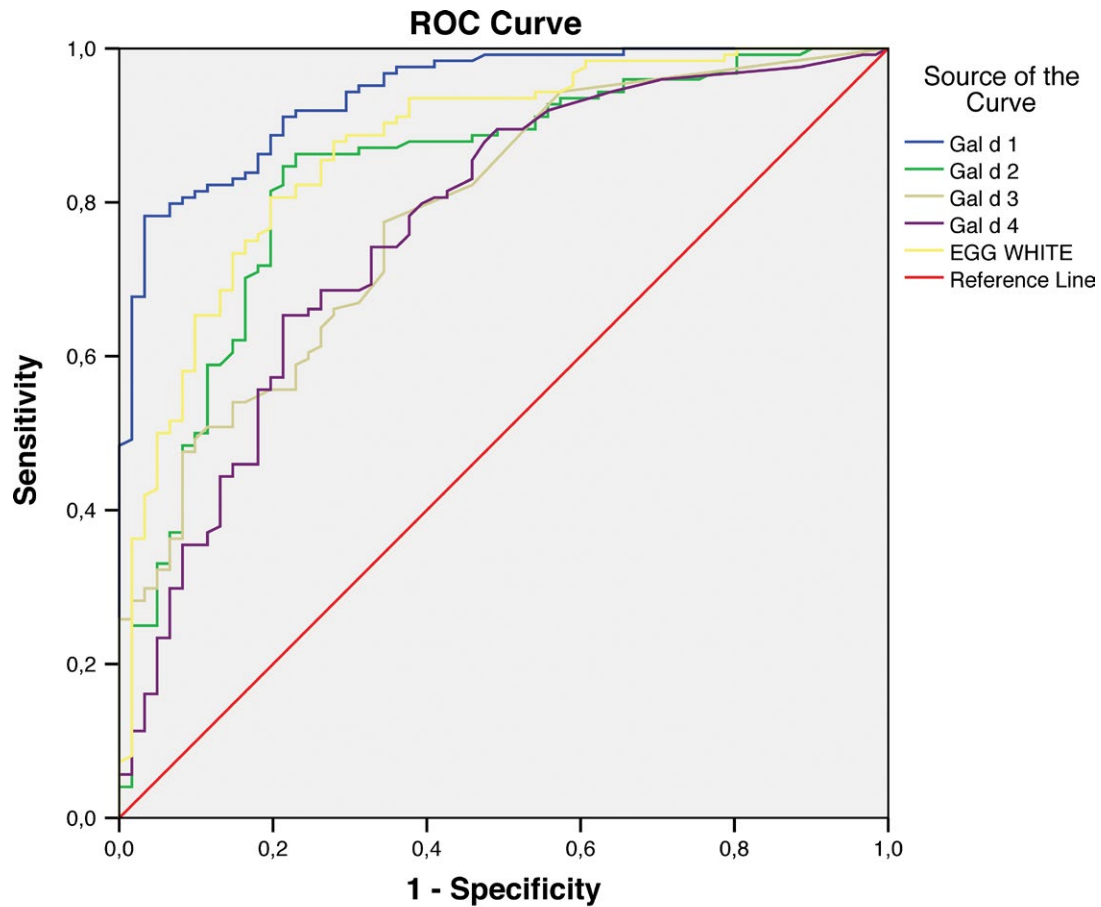
4 | DISCUSSION

This study, including 185 Finnish egg-sensitized children and adolescents, showed that Gal d 1 sIgE is useful in differentiating clinically reactive patients from those tolerant of heated egg. Gal d 1 sIgE with a cutoff of above 3.7 kU/L predicted a positive challenge outcome and a cutoff of below 0.9 kU/L a negative challenge outcome to heated egg with 95% probability. With a value of above 14 kU/L, all challenges were positive. There was no significant difference in the optimal cutoff for Gal d 1-specific IgE between the younger and older age groups. The diagnostic capacity of egg white sIgE was modest and slightly better than that of Gal d 2. Measurement of IgE to Gal d 3 or Gal d 4 was not useful in predicting the challenge outcome.

Published cutoffs predicting outcomes of egg challenges vary considerably. The proposed egg white sIgE cutoffs for positive raw egg challenges range from 1.2 to >99 kU/L and for heated egg challenges from 4.1 to 30.7 kU/L.¹⁸⁻²¹ Our results are in line with those published by Ando et al,¹⁹ who showed a strong correlation between egg white and Gal d 2 sIgE ($r = 0.97$). This is not surprising knowing that Gal d 2 constitutes up to 54% of the total egg white protein content.¹¹ We did not perform oral food challenges with raw egg and thus could not calculate decision points for raw egg challenges. Some authors have suggested that Gal d 1 IgE is more accurate than egg white in predicting raw egg allergy,^{19,22} while others have shown no advantage compared to egg white.^{8,22} A recent study from Denmark found that IgE to none of the allergenic components Gal d 1-4 was superior to egg white in predicting raw egg challenge outcomes in 130 children aged 8 months-8 years.¹³

Contradictory results have been published regarding the utility of Gal d 1 sIgE in the diagnosis of heated egg allergy. Vazquez-Ortiz et al²⁰ reported an identical Gal d 1 95% predictive decision point of 3.7 kU/L for heated egg challenges in 85 Spanish children aged 5-18 years, although the sensitivity (67%) and AUC in ROC curve (0.83) were lower. Alessandri et al¹⁴ performed DBPCFC with raw and heated egg white in 68 Italian children aged 1-11 years. On the ISAC microarray system, 44/47 (94%) of the Gal d 1 IgE-negative patients tolerated boiled egg. Two studies from Japan^{19,22} found Gal d 1 to be more accurate than egg white in the diagnosis of heated

FIGURE 2 Receiver operating characteristics (ROCs) in 185 patients and 95% predictive cutoff levels, sensitivity, specificity, and likelihood ratios for Gal d 1-4 and egg white specific IgE in different age groups. A. All 185 patients, B. 88 patients aged 1-5 y, and C. 97 patients aged 6-18 y

**(A) All 185 patients aged 1-18 y**

Specific IgE	AUC (95% CI)	Cutoff (kU/L)	Specificity %	Sensitivity %	Likelihood ratio
Gal d 1	0.94 (0.91 – 0.97)	3.7	95	78	15.9
Gal d 2	0.84 (0.77- 0.90)	14.9	95	33	6.7
Gal d 3	0.79 (0.72 -0.85)	2.4	95	35	6.6
Gal d 4	0.77 (0.69 – 0.85)	6.6	95	23	4.8
Egg white extract	0.87 (0.82 - 0.93)	13.2	95	50	10.2

(B) 88 patients aged 1-5 y

Specific IgE	AUC (95% CI)	Cutoff (kU/L)	Specificity %	Sensitivity %	Likelihood ratio
Gal d 1	0.93 (0.89 – 0.98)	3.8	95	71	16.6
Gal d 2	0.78 (0.68- 0.88)	4.4	95	37	5.2
Gal d 3	0.72 (0.61 -0.83)	0.7	95	19	4.5
Gal d 4	0.72 (0.61 – 0.83)	4.1	95	17	4.0
Egg white extract	0.85 (0.77 - 0.93)	19	95	34	8

(C) 97 patients aged 6-18 y

Specific IgE	AUC (95% CI)	Cutoff (kU/L)	Specificity %	Sensitivity %	Likelihood ratio
Gal d 1	0.93 (0.88 – 0.98)	3.5	95	84	11.8
Gal d 2	0.88 (0.79- 0.97)	10.8	95	45	6.2
Gal d 3	0.71 (0.59 -0.83)	4.4	95	37	5.2
Gal d 4	0.73 (0.59 – 0.87)	8.6	95	21	2.9
Egg white extract	0.87 (0.78 - 0.96)	13.1	95	55	7.8

egg allergy. Ando et al¹⁹ determined 95% predictive points in 108 Japanese children, aged 1-13 years, who all underwent DBPCFC with both raw and heated egg white. Egg white IgE was useful in predicting results of raw egg challenges, while Gal d 1 IgE was superior regarding heated egg challenges; the positive decision point was 10.8 kU/L, and the negative decision point was 1.2 kU/L. Haneda et al²² examined 100 Japanese children, aged 1-2 years, who underwent open egg challenges with boiled egg white; the 95% positive decision point for Gal d 1 IgE was 26.6 kU/L and for egg white 61.8 kU/L. In 54 South African egg-sensitized children,²³ Gal d 1 was the superior allergenic component in differentiating asymptomatic sensitization from allergy to moderately heated (scrambled) egg. In ROC analysis, the AUC for Gal d 1 was 0.83 in ImmunoCAP and 0.81 in ISAC. The most sensitive screening test was skin prick testing with fresh raw egg white.

Several studies from the United States have performed open egg challenges with extensively heated baked egg in a wheat matrix. Lemon-Mule⁸ and Caubet¹¹ found in 117 subjects aged 0.5-25 years that Gal d 1 was no better than egg white IgE in predicting challenge outcomes, although high (>50 kU/L) levels of Gal d 1 IgE predicted heated egg allergy. Likewise, Bartnikas²⁴ did not find Gal d 1 superior to egg white IgE in a retrospective study of 169 challenges performed in the office or at home.

Different and nonstandardized challenge protocols are likely to explain the discrepancy observed between the studies. The degree of heating and the presence of wheat in the matrix affect the allergenicity of egg proteins.²⁵ Heating reduces allergenicity by causing structural changes that destroy conformational IgE-binding epitopes present in unstable allergens including Gal d 2. Prolonged heating together with wheat flour, on the other hand, reduces the allergenicity of Gal d 1 by forming high molecular weight complexes with gluten that cause Gal d 1 aggregation and insolubilization.^{26,27} In line with these observations, the diagnostic performance of Gal d 1 sIgE has been considerably lower in studies where the challenge material contains wheat compared to studies using boiled egg white. Moreover, very high levels of Gal d 1 sIgE are needed to predict reactivity to heated egg in baked products containing wheat.⁸

We used egg white boiled for 10 minutes at 100°C in the open challenges and egg white powder masked in ground beef meatballs fried on the stove for 15 minutes in the DBPCFC. The matrix contained oatmeal and potato flour, but no wheat or gluten. The degree of heating was similar in both challenges. The patients above 6 years of age, who underwent DBPCFC, represented a selected group of patients with persistent egg allergy. They were evaluated for possible allergy resolution prior to eventual egg oral immunotherapy. The younger children aged 1-5 years probably included both those with persistent allergy and those who will develop tolerance in later life. Although the open and double-blind challenge protocols and patients' median ages differed (2.2 years vs 11.3 years), we found no significant differences in the predictive values between these two groups. Previous studies have linked acquisition of tolerance with decreasing IgE levels to egg white

and Gal d 1.^{6,13} Unfortunately, we did not have follow-up data on prior egg white and Gal d 1 sIgE levels, so we could not evaluate the effect of changes in sIgE levels.

Specific IgE to egg white or Gal d 1 did not predict symptom severity, allergen threshold doses, nor cumulative eliciting doses. Severe reactions were seen at all IgE levels and all doses. Thus, the clinical history is still the most important factor determining when to perform an oral challenge in an egg-sensitized patient. In the absence of a history of severe reactions, we suggest the following. With Gal d 1 sIgE below 0.9 kU/L, the patient can introduce heated egg into the diet at home. At levels between 1 and 3 kU/L, tolerance is probable and heated egg may carefully be challenged at home starting with small amounts. With Gal d 1 sIgE between 3 and 14 kU/L, we suggest a physician-supervised oral food challenge, and with levels above 14 kU/L, a positive reaction is so probable that no challenge is needed. For these patients, we suggest a strict elimination diet, precautionary medication, and follow-up of Gal d 1 IgE levels.

In summary, Gal d 1 sIgE appears useful in distinguishing egg-sensitized patients tolerant of heated egg. The optimal cutoff point for a positive challenge outcome in a Finnish population of 185 children and adolescents was 3.7 kU/L. Gal d 1 sIgE together with careful assessment of the clinical history can reduce the need for oral food challenges, but cannot be used in defining allergen threshold doses or reaction severity. Egg is a widely used ingredient worldwide, and up 70% of egg-allergic children tolerate heated egg. It is therefore important to identify the children able to free unnecessary dietary restrictions and introduce heated egg in their diet.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

1. Rona RJ, Keil T, Summers C, et al. The prevalence of food allergy: a meta-analysis. *J Allergy Clin Immunol*. 2007;120:638-646.
2. Nwaru BI, Hickstein L, Panesar SS, et al. Prevalence of common food allergies in Europe: a systematic review and meta-analysis. *Allergy*. 2014;69:992-1007.
3. Bekkers MB, Aalberse RC, Gehring U, et al. Hen's egg, not cow's milk, sensitization in infancy is associated with asthma: 10-year follow-up of the PIAMA birth cohort. *J Allergy Clin Immunol*. 2013;132:1427-1428.
4. Nickel R, Kulig M, Forster J, et al. Sensitization to hen's egg at the age of twelve months is predictive for allergic sensitization to common indoor and outdoor allergens at the age of three years. *J Allergy Clin Immunol*. 1997;99:613-617.
5. Sicherer SH, Wood RA, Vickery BP, et al. The natural history of egg allergy in an observational cohort. *J Allergy Clin Immunol*. 2014;133:492-499.e8.

6. Ohtani K, Sato S, Syukuya A, et al. Natural history of immediate-type hen's egg allergy in Japanese children. *Allergol Int*. 2016;65:153-157.
7. Des Roches A, Nguyen M, Paradis L, Primeau M, Singer S. Tolerance to cooked egg in an egg allergic population. *Allergy*. 2006;61:900-901.
8. Lemon-Mulé H, Sampson HA, Sicherer SH, Shreffler WG, Noone S, Nowak-Węgrzyn A. Immunologic changes in children with egg allergy ingesting extensively heated egg. *J Allergy Clin Immunol*. 2008;122:977-983.e1.
9. Leonard SA, Sampson HA, Sicherer SH, et al. Dietary baked egg accelerates resolution of egg allergy in children. *J Allergy Clin Immunol*. 2012;130:473-480.e1.
10. Clark A, Islam S, King Y, et al. A longitudinal study of resolution of allergy to well-cooked and uncooked egg. *Clin Exp Allergy*. 2011;41:706-712.
11. Caubet JC, Bencharitiwong R, Moshier E, Godbold JH, Sampson HA, Nowak-Węgrzyn A. Significance of ovomucoid- and ovalbumin-specific IgE/IgG4 ratios in egg allergy. *J Allergy Clin Immunol*. 2012;129:739-747.
12. Järvinen KM, Beyer K, Vila L, Bardina L, Mishoe M, Sampson HA. Specificity of IgE antibodies to sequential epitopes of hen's egg ovomucoid as a marker for persistence of egg allergy. *Allergy*. 2007;62:758-765.
13. Gradman J, Mortz CG, Eller E, Bindslev-Jensen C. Relationship between specific IgE to egg components and natural history of egg allergy in Danish children. *Pediatr Allergy Immunol*. 2016;27:825-830.
14. Alessandri C, Zennaro D, Scala E, et al. Ovomucoid (Gal d 1) specific IgE detected by microarray system predict tolerability to boiled hen's egg and an increased risk to progress to multiple environmental allergen sensitisation. *Clin Exp Allergy*. 2012;42:441-450.
15. Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol*. 2001;107:891-896.
16. Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. *J Allergy Clin Immunol*. 2012;130:1260-1274.
17. Kukkonen AK, Pelkonen AS, Mäkinen-Kiljunen S, Voutilainen H, Mäkelä MJ. Ara h 2 and Ara 6 are the best predictors of severe peanut allergy: a double-blind placebo-controlled study. *Allergy*. 2015;70:1239-1245.
18. Komata T, Söderström L, Borres MP, Tachimoto H, Ebisawa M. The predictive relationship of food-specific serum IgE concentrations to challenge outcomes for egg and milk varies by patient age. *J Allergy Clin Immunol*. 2007;119:1272-1274.
19. Ando H, Movérare R, Kondo Y, et al. Utility of ovomucoid-specific IgE concentrations in predicting symptomatic egg allergy. *J Allergy Clin Immunol*. 2008;122:583-588.
20. Vazquez-Ortiz M, Alvaro M, Piquer M, et al. Predicting reactions severity at challenge in egg-allergic patients. *Clin Exp Allergy*. 2014;44:1096-1097.
21. Calvani M, Arasi S, Bianchi A, et al. Is it possible to make a diagnosis of raw, heated, and baked egg allergy in children using cutoffs? A systematic review. *Pediatr Allergy Immunol*. 2015;26:509-521.
22. Haneda Y, Kando N, Yasui M, et al. Ovomucoids IgE is a better marker than egg white-specific IgE to diagnose boiled egg allergy. *J Allergy Clin Immunol*. 2012;129:1681-1682.
23. Gray CL, Levin ME, du Toit G. Egg sensitization, allergy and component patterns in African children with atopic dermatitis. *Pediatr Allergy Immunol*. 2016;27:709-715.
24. Bartnikas LM, Sheehan WJ, Larabee KS, Petty C, Schneider LC, Phipatanakul W. Ovomucoid is not superior to egg white testing in predicting tolerance to baked egg. *J Allergy Clin Immunol*. 2013;135:354-360.e2.
25. Bloom KA, Huang FR, Bencharitiwong R, et al. Effect of heat treatment on milk and egg proteins allergenicity. *Pediatr Allergy Immunol*. 2014;25:740-746.
26. Kato Y, Watanabe H, Matsuda T. Ovomucoid rendered insoluble by heating with wheat gluten but not with milk casein. *Biosci Biotechnol Biochem*. 2000;64:198-201.
27. Shin M, Han Y, Ahn K. The influence of the time and temperature of heat treatment on the allergenicity of egg white proteins. *Allergy Asthma Immunol Res*. 2013;5:96-101.

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