

The Clinical Usefulness of IgE Antibodies Against Egg White and Its Components in Korean Children

Taek Ki Min, You Hoon Jeon, Hyeon Jong Yang, Bok Yang Pyun*

Pediatric Allergy and Respiratory Center, Department of Pediatrics, Soonchunhyang University Hospital, Seoul, Korea

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Purpose: Egg (egg white) allergies are among the most common food allergies in infants and young children. Serum egg white-specific IgE (sIgE) levels have been shown to be correlated with clinical symptoms, and the predictive decision point of sIgE levels has been proposed and used widely in the clinical setting. However, some patients whose sIgE levels to egg white are higher than the predictive decision point value show no clinical symptoms, and vice versa. This study was conducted to evaluate the clinical usefulness of sIgE antibodies to egg white and its components in the diagnosis of egg allergies. **Methods:** Forty-one patients younger than 2 years of age with no experience of egg intake due to concerns regarding allergies or a non-specific clinical response to eggs were enrolled. Total IgE levels and the levels of IgE antibodies specific for egg white and its components (ovomucoid, ovalbumin, and conalbumin) were measured by ImmunoCAP testing. The clinical response of the subjects was confirmed by an open oral food challenge (OFC). **Results:** Fifteen (71.4%) out of 21 patients in the egg white-sIgE ≥ 2 kU/L group showed a positive response, while 10 (50.0%) out of 20 patients in the egg white-sIgE < 2 kU/L group showed a negative response to the OFC. There were no statistically significant differences in the levels of sIgE antibodies against egg white and its components between the positive and negative open OFC groups. In addition, there were no statistically significant differences in the levels of sIgE antibodies against egg white and its components based on an intra-group analysis. **Conclusions:** Our results show that the sensitivity and specificity of the predictive decision point values for egg white-sIgE antibodies by ImmunoCAP were relatively low in Korean children. In addition, no egg white component predicted the clinical reactivity of the subjects. We suggest that the predictive decision point value for a positive egg oral challenge test by ImmunoCAP should be re-evaluated. Moreover, we suggest that careful personal history recording and challenge tests are necessary for the correct diagnosis of an egg allergy.

Key Words: Egg hypersensitivity; egg white proteins

INTRODUCTION

Egg allergies are among the most common food allergies in infants and young children.¹⁻³ A recent meta-analysis of the prevalence of food allergies estimated that egg allergies affect 0.5%-2.5% of young children.⁴ Egg white is often responsible for the early development of urticaria and eczema during infancy. In some cases, life threatening or fatal anaphylactic reactions can occur.⁵ Therefore, it is important to confirm the diagnosis of an egg allergy, as treatment requires the elimination of eggs from the diet.

Egg allergies are currently diagnosed based on the patient's clinical history, a physical examination, a skin prick test, and the presence of IgE antibodies specific for egg white; however, the condition can only be verified through an oral challenge test.³ Serum egg white-specific IgE (sIgE) levels have been shown to be correlated with the outcome of oral challenge tests,⁶ and predictive decision point values for sIgE antibodies have been de-

termined and are widely used in clinical settings.^{7,8} However, some patients with egg-sIgE antibody levels that are higher than the predictive decision point values show no clinical symptoms, and vice versa.

Egg white contains several allergenic proteins, including ovomucoid (Gal d 1, 11%), ovalbumin (Gal d 2, 55%), conalbumin (Gal d 3, 12%), lysozyme (Gal d 4, 3%), and ovomucin (4%).⁹ Although ovalbumin is the most abundant protein in egg white, ovomucoid has been shown to be the dominant allergen in eggs.¹⁰ It has been reported that ovomucoid-sIgE antibody levels can be used to predict whether children can tolerate heat-

Correspondence to: Bok Yang Pyun, MD, PhD, Pediatric Allergy and Respiratory Center, Department of Pediatrics, Soonchunhyang University Hospital, 22 Daesagwan-gil, Yongsan-gu, Seoul 140-743, Korea.
Tel: +82-2-709-9339; Fax: +82-2-794-5471; E-mail: bypyun@schmc.ac.kr
Received: July 11, 2012; Revised: September 28, 2012; Accepted: October 23, 2012

• There are no financial or other issues that might lead to conflict of interest.

treated eggs (e.g., in baked goods) and outgrow their egg allergy.^{11,12} In addition, it has been suggested that the quantification of ovomucoid-sIgE antibodies can be useful in helping physicians decide whether to perform an oral food challenge (OFC).¹³

This study was conducted to further evaluate the clinical reactivity and diagnostic value of the measurement of IgE antibodies specific for egg white and its components.

MATERIALS AND METHODS

Study population

This prospective study included children younger than 2 years of age who visited the Pediatric Allergy and Respiratory Center of Soonchunhyang University Hospital (a tertiary medical center in Seoul, Korea) from 1 January 2010 to 31 May 2011. They were evaluated for an egg allergy as a cause of atopic dermatitis or food allergy symptoms. The subjects included 41 infants (22 [53.7%] males; median age, 16 months; range, 3-23 months) with no experience of egg intake due to concerns regarding egg allergies or with a non-specific clinical response to egg intake. Subjects were excluded from the study if they had a history of anaphylaxis or unstable asthma and if they had used antihistamines more than once within 3-10 days of the challenge. The study protocol was approved by the Institutional Review Board of Soonchunhyang University Hospital; informed consent was obtained before enrollment.

Measurement of the total IgE and sIgE antibody levels

Serum samples were obtained from all patients prior to the food challenge. The total IgE levels and levels of IgE antibodies specific for egg white, ovalbumin, ovomucoid, conalbumin, and eosinophil cationic protein (ECP) were measured using ImmunoCAP testing according to the manufacturer's instructions (Phadia AB, Uppsala, Sweden).

Challenge test

An open OFC with egg white was performed at the Pediatric Allergy and Respiratory Center under the supervision of a physician and with previous parental authorization. The challenge was performed using cooked (15 minutes of boiling) egg white.

The initial challenge dose corresponded to 1 mg of egg white. The dose was increased based on the logarithmic mean (e.g., 1, 3, 10, and 30) until the maximum dose was reached or the patient reacted. The patients fasted for at least 4 hours prior to the OFC when immediate reactions were anticipated and for 12 hours when late reactions were anticipated. The specific criteria for the diagnostic challenge test were as described previously.¹⁴ The test was administered according to standard guidelines for OFC testing,¹⁴ except for in children with a history of severe anaphylaxis.

Statistical analysis

The patients were assigned to one of two groups according to their egg white-sIgE level, considering the positive decision point value (group I, ≥ 2 kU_A/L; group II, < 2 kU_A/L),¹⁵ and each group was divided according to the results of the OFC (positive, group A; negative, group B). Descriptive statistics were used to determine the frequencies of all qualitative variables and the median value for most quantitative variables. The results were expressed using the median value, with interquartile ranges (25th-75th percentile) (IQR) because of the asymmetric distribution of sIgE antibodies for egg white and its components and the total IgE level. The Mann-Whitney U test was used for the pairwise comparison of continuous parameters (age, total IgE and sIgE concentrations, and ECP level) between the study groups. All calculated *P* values were 2-sided, and *P* values less than 0.05 were considered statistically significant. The analysis was performed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

All patients included in our study underwent blood tests and an open OFC. A total of 15 (71.4%) out of 21 patients in group I showed a positive response, while 10 (50.0%) out of 20 patients in group II showed a negative response to the OFC. No significant differences in the total IgE or ECP level were detected by an intra-group comparison (Table 1).

The median concentration of egg white-sIgE antibodies was 10.90 kU/L (IQR 7.34-77.70) in the OFC-positive and egg white-

Table 1. Characteristics of the 41 children enrolled in the study

	Group I (n=21)			Group II (n=20)		
	Group IA (n=15)	Group IB (n=6)	<i>P</i> value	Group IIA (n=10)	Group IIB (n=10)	<i>P</i> value
Sex (males)	8 (53.3%)	2 (33.3%)	0.66	6 (60.0%)	6 (60.0%)	1.00
Age (months)	16.0 (15.0-19.0)	17.0 (8.3-22.5)	0.88	15.5 (10.8-18.5)	18.0 (14.8-19.0)	0.40
Total IgE (kU/L)	176.0 (72.9-1097.0)	212.5 (59.5-434.8)	0.59	69.3 (30.3-91.0)	48.0 (20.4-112.8)	0.70
ECP (μg/L)	10.5 (2.3-15.1)	18.9 (10.8-28.5)	0.24	15.3 (7.5-23.3)	9.8 (7.1-19.6)	0.60

All values are presented as the number (%) or median (interquartile range).

Group I: egg white-sIgE ≥ 2 kU_A/L; group II: < 2 kU_A/L. Group A: OFC positive; group B: OFC negative. OFC, oral food challenge; ECP, eosinophil cationic protein.

Table 2. Intra-group comparison of the levels of IgE antibodies against egg white and its components

sIgE (kU _A /L)	Group I (n=21)			Group II (n=20)		
	Group IA (n=15)	Group IB (n=6)	P value	Group IIA (n=10)	Group IIB (n=10)	P value
Egg white	10.90 (7.34-77.70)	11.95 (3.44-49.10)	0.48	1.29 (0.92-1.54)	0.88 (0.55-1.36)	0.17
Ovomucoid	10.90 (1.70-26.40)	4.43 (2.47-6.78)	0.27	1.16 (0.34-1.42)	0.42 (0.27-0.95)	0.33
Ovalbumin	5.77 (0.66-38.10)	0.96 (0.13-32.90)	0.39	0.41 (0.14-0.92)	0.07 (0.03-0.89)	0.60
Conalbumin	0.43 (0.14-2.23)	0.16 (0.04-7.09)	0.20	0.03 (0.01-0.04)	0.03 (0.01-0.07)	0.79

All values are presented as the median (interquartile range).
 Group I: egg white-sIgE ≥ 2 kU_A/L; group II: < 2 kU_A/L. Group A: OFC positive; group B: OFC negative.
 sIgE, specific immunoglobulin E; OFC, oral food challenge.

Table 3. Performance characteristics of egg white-sIgE antibodies at a cut-off level of 2 kU_A/L

	OFC (+)	OFC (-)	
sIgE ≥ 2 kU _A /L	15	6	Positive predictive value (71.4%)
sIgE < 2 kU _A /L	10	10	Negative predictive value (50.0%)
	Sensitivity 60.0%	Specificity 62.5%	

sIgE, specific immunoglobulin E; OFC, oral food challenge.

sIgE ≥ 2 kU_A/L group (group IA), 11.95 kU/L (IQR 3.44-49.10) in the OFC-negative and egg white-sIgE ≥ 2 kU_A/L group (group IB), 1.29 kU/L (IQR 0.92-1.54) in the OFC-positive and egg white-sIgE < 2 kU_A/L group (group IIA), and 0.88 kU/L (IQR 0.55-1.36) in the OFC-negative and egg white-sIgE < 2 kU_A/L group (group IIB). The median concentration of ovomucoid-sIgE antibodies was 10.90 kU/L (IQR 1.70-26.40) in group IA, 4.43 kU/L (IQR 2.47-6.78) in group IB, 1.16 kU/L (IQR 0.34-1.42) in group IIA, and 0.42 kU/L (IQR 0.27-0.95) in group IIB. There were no statistically significant differences in the levels of sIgE antibodies against egg white, ovomucoid, and other egg white components based on an intra-group analysis (Table 2).

In addition, there were no statistically significant differences in the levels of sIgE antibodies against egg white (5.12 vs. 1.44 kU_A/L, P=0.054), ovomucoid (1.70 vs. 1.00 kU_A/L, P=0.165), or other egg white components between the OFC-positive and -negative groups (Figure). The positive and negative predictive values of the positive decision point (egg white-sIgE ≥ 2 kU_A/L) were very low (71.4 and 50.0%, respectively; Table 3).

DISCUSSION

The diagnostic workup for a suspected food allergy should start with a detailed history and physical examination of the patient.⁸ The next step may include a skin test, blood test, or both; the detection of allergen-sIgE antibodies provides confirmation of sensitization, which strengthens the diagnosis.⁸ Egg white-sIgE antibodies can be measured quantitatively using standardized

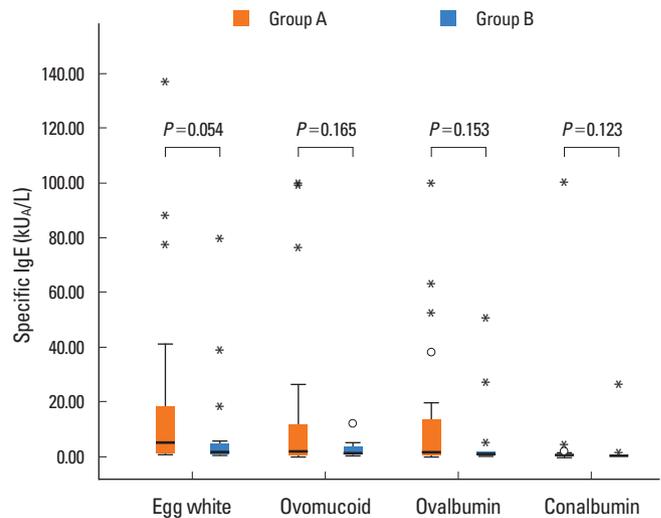


Figure. Comparison of the levels of specific immunoglobulin E (sIgE) antibodies against egg white and its components between the oral food challenge (OFC)-positive (A) and -negative (B) groups.

in vitro assays. There is a positive correlation between increasing levels of egg white-sIgE antibodies and the likelihood of clinical reactivity to eggs.¹⁶ It has been suggested that the quantification of sIgE antibodies to egg white could help physicians decide whether to perform an OFC. Studies using the ImmunoCAP system (Phadia AB) have shown that an egg-sIgE level of 7 kU_A/L has a 95% positive predictive value (PPV) for clinical reactivity to egg in children more than 2 years of age; in children 2 years of age or less, a level of 2 kU_A/L has a 95% PPV.^{17,18} However, there is poor agreement between the cutoff levels identified by different centers.^{6,19-22}

We also found that there was no correlation between the presence of symptoms and the level of sIgE antibodies to egg white. The sensitivity and specificity of the positive decision point value for egg white-sIgE antibodies (2 kU_A/L) by ImmunoCAP testing was relatively low (60.0 and 62.5%) in Korean children younger than 2 years of age. This may be because of differences in the inclusion criteria, significance level, challenge method and outcome criteria, subject age, and prevalence of an egg allergy and eczema between the studies. These variables should be taken

into account when interpreting cutoff levels for any given patient population. The measurement of sIgE antibodies to egg whites in the absence of a history of egg ingestion is discouraged because the test has poor sensitivity and a low negative predictive value. The presence of undetectable IgE levels to egg (<0.35 kU_A/L) does not exclude clinical reactivity to eggs.^{16,17} Therefore, when sIgE measures are inconsistent with the clinical history, an OFC is the most reliable indicator of food hypersensitivity.²³

Egg component proteins differ in their physical properties and may be related to different clinical patterns of egg allergy.⁸ The term “component-resolved diagnosis” is used to designate diagnostic tests based on pure allergen molecules, which are produced either by the recombinant expression of allergen-encoding cDNAs or purification from natural allergen sources.²⁴ The measurement of IgE antibodies specific for individual egg white components could be of importance in predicting different disease manifestations in egg-allergic patients.⁸ Although ovalbumin is the most abundant protein found in egg white, it is sensitive to thermal denaturation, with a resultant decrease in allergenicity.²⁵ In contrast, ovomucoid possesses unique characteristics, including relative stability against heat²⁶ and digestion with proteinases²⁷ and strong allergenicity⁹ as compared with other egg white components. This is possibly related to the presence of disulfide bonds, which stabilize the protein.¹⁰ A recent study demonstrated that the quantitative measurement of sIgE antibodies, both toward egg white and ovomucoid, was useful in the management of children with an egg allergy.¹³ However, we could not demonstrate any association between the levels of sIgE antibodies to individual egg white components and clinical reactivity to egg whites.

Previous studies indicated that tolerance to eggs is achieved by most children with an egg allergy, with resolution in 50% of cases by 3 years of age and in 66% of cases by 5 years of age.¹⁵ However, a more recent study suggested that egg allergies are more persistent, predicting resolution in 4% of cases by 4 years of age, 12% by 6 years of age, 37% by 10 years of age, and 68% by 16 years of age.²⁸ Whether these differing results are caused by population differences or a change in the natural history of the egg allergy is unclear. Several prognostic factors for the development of tolerance to eggs have been identified, including a lower level of egg-sIgE antibodies, a higher rate of decline in egg-sIgE antibodies with time, and an earlier age at diagnosis.²⁹

In conclusion, we suggest that the predictive decision point value for a positive egg oral challenge test by ImmunoCAP should be re-evaluated and that an OFC is necessary in order to correctly diagnose an egg allergy. Additional studies are needed to predict the severity of allergic reactions that may occur for each individual and given the natural history of the allergy.

REFERENCES

1. Eggesbø M, Botten G, Halvorsen R, Magnus P. The prevalence of al-

- lergy to egg: a population-based study in young children. *Allergy* 2001;56:403-11.
2. Heine RG, Laske N, Hill DJ. The diagnosis and management of egg allergy. *Curr Allergy Asthma Rep* 2006;6:145-52.
3. Sicherer SH, Sampson HA. 9. Food allergy. *J Allergy Clin Immunol* 2006;117:S470-5.
4. Rona RJ, Keil T, Summers C, Gislason D, Zuidmeer L, Sodergren E, Sigurdardottir ST, Lindner T, Goldhahn K, Dahlstrom J, McBride D, Madsen C. The prevalence of food allergy: a meta-analysis. *J Allergy Clin Immunol* 2007;120:638-46.
5. Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. *N Engl J Med* 1992;327:380-4.
6. 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;119:1272-4.
7. Sampson HA. Update on food allergy. *J Allergy Clin Immunol* 2004;113:805-19; quiz 820.
8. Caubet JC, Wang J. Current understanding of egg allergy. *Pediatr Clin North Am* 2011;58:427-43, xi.
9. Bernhisel-Broadbent J, Dintzis HM, Dintzis RZ, Sampson HA. Allergenicity and antigenicity of chicken egg ovomucoid (Gal d III) compared with ovalbumin (Gal d I) in children with egg allergy and in mice. *J Allergy Clin Immunol* 1994;93:1047-59.
10. Cooke SK, Sampson HA. Allergenic properties of ovomucoid in man. *J Immunol* 1997;159:2026-32.
11. Urisu A, Ando H, Morita Y, Wada E, Yasaki T, Yamada K, Komada K, Torii S, Goto M, Wakamatsu T. Allergenic activity of heated and ovomucoid-depleted egg white. *J Allergy Clin Immunol* 1997;100:171-6.
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;62:758-65.
13. Ando H, Movérare R, Kondo Y, Tsuge I, Tanaka A, Borres MP, Urisu A. Utility of ovomucoid-specific IgE concentrations in predicting symptomatic egg allergy. *J Allergy Clin Immunol* 2008;122:583-8.
14. Nowak-Węgrzyn A, Assa'ad AH, Bahna SL, Bock SA, Sicherer SH, Teuber SS; Adverse Reactions to Food Committee of American Academy of Allergy, Asthma & Immunology. Work Group report: oral food challenge testing. *J Allergy Clin Immunol* 2009;123:S365-83.
15. Boyano-Martínez T, García-Ara C, Díaz-Pena JM, Martín-Esteban M. Prediction of tolerance on the basis of quantification of egg white-specific IgE antibodies in children with egg allergy. *J Allergy Clin Immunol* 2002;110:304-9.
16. Perry TT, Matsui EC, Kay Conover-Walker M, Wood RA. The relationship of allergen-specific IgE levels and oral food challenge outcome. *J Allergy Clin Immunol* 2004;114:144-9.
17. Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol* 2001;107:891-6.
18. Boyano Martínez T, García-Ara C, Díaz-Pena JM, Muñoz FM, García Sánchez G, Esteban MM. Validity of specific IgE antibodies in children with egg allergy. *Clin Exp Allergy* 2001;31:1464-9.
19. Osterballe M, Bindslev-Jensen C. Threshold levels in food challenge and specific IgE in patients with egg allergy: is there a relationship? *J Allergy Clin Immunol* 2003;112:196-201.
20. Sampson HA, Ho DG. Relationship between food-specific IgE con-

- centrations and the risk of positive food challenges in children and adolescents. *J Allergy Clin Immunol* 1997;100:444-51.
21. Celik-Bilgili S, Mehl A, Verstege A, Staden U, Nocon M, Beyer K, Niggemann B. The predictive value of specific immunoglobulin E levels in serum for the outcome of oral food challenges. *Clin Exp Allergy* 2005;35:268-73.
 22. Benhamou AH, Zamora SA, Eigenmann PA. Correlation between specific immunoglobulin E levels and the severity of reactions in egg allergic patients. *Pediatr Allergy Immunol* 2008;19:173-9.
 23. Sampson HA. Food allergy--accurately identifying clinical reactivity. *Allergy* 2005;60 Suppl 79:19-24.
 24. Valenta R, Lidholm J, Niederberger V, Hayek B, Kraft D, Grönlund H. The recombinant allergen-based concept of component-resolved diagnostics and immunotherapy (CRD and CRIT). *Clin Exp Allergy* 1999;29:896-904.
 25. Joo K, Kato Y. Assessment of allergenic activity of a heat-coagulated ovalbumin after in vivo digestion. *Biosci Biotechnol Biochem* 2006;70:591-7.
 26. Honma K, Aoyagi M, Saito K, Nishimuta T, Sugimoto K, Tsunoo H, Niimi H, Kohno Y. Antigenic determinants on ovalbumin and ovomucoid: comparison of the specificity of IgG and IgE antibodies. *Arerugi* 1991;40:1167-75.
 27. Matsuda T, Watanabe K, Nakamura R. Immunochemical and physical properties of peptic-digested ovomucoid. *J Agric Food Chem* 1983;31:942-6.
 28. Savage JH, Matsui EC, Skripak JM, Wood RA. The natural history of egg allergy. *J Allergy Clin Immunol* 2007;120:1413-7.
 29. Shek LP, Soderstrom L, Ahlstedt S, Beyer K, Sampson HA. Determination of food specific IgE levels over time can predict the development of tolerance in cow's milk and hen's egg allergy. *J Allergy Clin Immunol* 2004;114:387-91.