Original Article

Ovomucoid Is Not Superior to Egg White Testing in Predicting Tolerance to Baked Egg

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What is already known about this topic? Children with egg allergy may tolerate baked egg products. Ovomucoid specific IgE antibody levels have been suggested to predict outcomes of baked egg challenges.

What does this article add to our knowledge? Measurement of specific IgE to ovomucoid may aid, together with egg white specific IgE and skin prick test, in predicting outcomes of baked egg challenges. No single measure appears superior.

How does this study impact current management guidelines? Specific IgE to ovomucoid, a heat-stable allergen, is a useful but not superior immunologic marker for predicting baked egg tolerance. Egg white specific IgE and skin prick testing remain important predictors of baked egg tolerance.

BACKGROUND: Children with egg allergy may tolerate baked egg products. Ovomucoid specific IgE (sIgE) antibody levels have been suggested to predict outcomes of baked egg challenges.

OBJECTIVE: We determined the relationship of ovomucoid and egg white sIgE levels and egg white skin prick test (SPT) wheal size with baked egg challenge outcome.

METHODS: Retrospective review of 1186 patients who underwent ovomucoid sIgE blood testing. Subset analysis was of 169 patients who underwent baked egg food challenges.

RESULTS: Egg white sIgE, ovomucoid sIgE, and egg white SPT were different among those eating regular egg, eating baked egg only, or avoiding all egg ($P < .001$ for all). One hundred forty-two of 169 patients (84.0%) passed baked egg challenges. We were able to establish >90% predictive values for passing baked egg challenge for egg white sIgE, ovomucoid sIgE, and egg white SPT. No patient with egg white SPT wheal <3 mm failed a baked egg challenge. Receiver operating characteristic curve analysis of egg white sIgE, ovomucoid sIgE, and egg white SPT showed areas under the curve of 0.721, 0.645, and 0.624, respectively. No significant difference was observed among these immunologic parameters in their abilities to predict baked egg challenge outcome ($P = .301$).

CONCLUSION: Most children with egg allergy in this study passed baked egg challenges. Ovomucoid sIgE, although a useful clinical predictor of baked egg tolerance, was not superior to egg white SPT or sIgE in predicting outcome of baked egg challenge. **(J Allergy Clin Immunol: In Practice 2013;1:354-60)**

Key words: *Egg allergy; Baked egg; Heated egg; Ovomucoid; Egg white; Food challenge*

Hen's egg allergy is a common cause of childhood food allergy, affecting 1% to 2% of children,[1-3] and is the most common food allergy in children with atopic dermatitis.[4,5] Although most children will develop tolerance to egg, children are outgrowing their egg allergies at later ages than previously reported.[6] Recent evidence suggests that 70% to 80% of children with egg allergy tolerate baked egg products.[7-10] Tolerance to baked egg may be achieved more rapidly than to regular egg.[11] Chileren with egg allergy who regularly consume baked egg may outgrow their egg allergies earlier than those strictly avoiding egg.[12] Immunologic changes in children incorporating baked egg into their diets include decreased egg protein specific IgE (sIgE) levels and skin prick test (SPT) wheal diameters and increased egg protein specific IgG_4 levels.[10,12]

Egg white contains >20 glycoproteins, with ovomucoid, ovalbumin, ovotransferrin, and lysozyme identified as the main allergens. Although ovalbumin is the most abundant protein in egg white, ovomucoid is the dominant allergen. Exposing proteins

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Abbreviations used
ARC- Allergic rhinoconjunctivitis
AUC- Area under the curve
EoE- Eosinophilic esophagitis
NPV- Negative predictive value
PPV- Positive predictive value
ROC- Receiver operating characteristic
sIgE- Specific IgE
SPT- Skin prick test

to high temperatures through baking reduces allergenicity by destroying conformational epitopes. In addition, allergenicity may be decreased by blocking epitope access through interaction with other food proteins, such as in a wheat matrix in a baked muffin or cupcake.[13] The importance of ovomucoid as an allergen may be related to its stability against heat and digestion with proteinases.[14]

Several studies have reported the importance of ovomucoid sIgE in predicting baked egg tolerance.[10,15-18] Further, Ando et al[15] suggested that ovomucoid sIgE was superior to egg white sIgE in predicting the outcome of heated egg challenge. Taken together, these studies suggest that measurement of sIgE to the heat-stable allergen, ovomucoid, may be an important diagnostic tool in predicting baked egg tolerance. We sought to determine whether ovomucoid sIgE was a superior predictor of tolerance to baked egg.

METHODS

Study design

A retrospective chart review was performed of all patients who underwent blood testing for ovomucoid sIgE at Boston Children's Hospital during an 18-month period from April 2010 through September 2011. Egg white SPT results, total IgE, egg white sIgE levels, clinical history, demographics, and food challenge outcomes were obtained through medical record review. Current egg ingestion practice at the time of ovomucoid sIgE blood test was determined by physician-documented parental report. Current egg ingestion practice was the result of physician recommendation, prior food challenge outcome, or patient-initiated food avoidance or introduction. Patients were excluded from analysis of egg ingestion practices and food challenge outcomes if they had eosinophilic esophagitis (EoE), because the significance of IgE sensitization to foods in EoE is not well understood.[19] The study was approved by the Institutional Review Board of Boston Children's Hospital.

Allergy evaluation

SPT were performed according to previously published methods[20] with the use of the Multi-Test device (Alk-Abello, Round Rock, Texas) and commercially prepared extracts (Greer Laboratories, Lenoir, NC). Control tests for SPT were performed with histamine (positive control) and normal saline (negative control). Wheal diameters were measured 15 minutes after the skin test was placed, in a standard fashion.[20] A SPT wheal diameter at least 3 mm larger than the negative control was considered positive.[21]

Serum samples were analyzed for sIgE with the use of an ImmunoCAP fluorescence enzyme immunoassay (Thermo Scientific, Portage, Mich). The lowest limit of detection of the assay was 0.35 kU/L, and the highest limit of detection was 100 kU/L.

Oral challenge

Food challenges were performed as open challenges, either under physician supervision at Boston Children's Hospital or at home. Blood and SPT results were obtained within 1 year before the food challenge or, in cases of some failed challenges, the most recent result after challenge failure, medians (interquartile range) 2.28 (−1.56 to 6.13) and 2.30 (−1.41 to 6.02) months, respectively. In the case of a negative number, the blood or SPT result was obtained a given time after a failed challenge. One hundred sixty-seven of 169 patients (98.8%) challenged to baked egg had a history of prior allergic reactions to egg (either baked or regular) documented in the medical record by an allergist and/or egg sensitization, as determined by a positive SPT or elevated serum sIgE. Two patients challenged to baked egg had negative egg protein sIgE and SPT and no prior history of ingestion but had evaluation performed because of personal history of other food allergies.[21] We elected to include patients who were avoiding egg due to atopic dermatitis in our analysis, because testing for food allergies in children with atopic dermatitis is reasonable in specific circumstances.[21]

Patients were considered for baked egg challenge in clinic if egg white SPT wheal was <35 mm and ovomucoid sIgE was <4.00 kU/L, based on previously suggested guidelines.[8] Patients were considered for baked egg challenge at home if egg white SPT wheal was <7 mm and ovomucoid sIgE was <1.00 kU/L.[8,15] Patients with a history of anaphylaxis to baked egg within the past 2 years or unstable asthma were not recommended for food challenges. However, the decision for ordering and determining location (clinic or home) of the food challenge was ultimately at the discretion of the ordering allergist. The physician-supervised baked egg challenge was performed in a standard fashion according to previously published methods.[8,10] Parents were instructed to prepare muffins or cupcakes at home according to a protocol that our clinic provided. The recipe contained two large eggs, including both egg white and yolk. Each muffin or cupcake contained one-third of an egg (approximately 2.2 g of egg protein). The muffins or cupcakes were baked at 350°F in an oven for 30 minutes. A standard graded open food challenge consisted of increasing increments every 15 minutes of one-eighth (275 mg), one-fourth (550 mg), and five-eighths (1375 mg) muffin or cupcake, totaling 2.2 g of egg protein. For home challenges, parents were instructed to introduce baked egg in a manner similar to the clinic challenge protocol.

For physician-supervised challenges, patients were monitored throughout and for 30 to 60 minutes after the completion of the challenge. Challenges were discontinued at the first objective sign of reaction,[21] and treatment was initiated at the discretion of the supervising physician. Home challenges were terminated, and treatment was initiated at the discretion of the parent.

Statistical analysis

Outcome of oral food challenge was used as the "gold standard" by which performance characteristics (sensitivity, specificity, positive predictive value [PPV], and negative predictive value [NPV]) were calculated. The PPV refers to an egg white sIgE, ovomucoid sIgE, or egg white SPT level above which it is a given percentage likely that a patient will react and therefore have a failed food challenge outcome. The NPV refers to a level below which it is a given percentage likely that a patient will not react and therefore have a passed food challenge outcome.[22] Receiver operating characteristic (ROC) curve analysis was used