

Original article

Utility of the ratio of food-specific IgE/total IgE in predicting symptomatic food allergy in children

Background: Double-blind, placebo-controlled food challenges are time-consuming, expensive and not without risk to patients. Therefore, an *in vitro* test that could accurately diagnose food allergy would be of great value.

Objective: To evaluate the utility of the ratio of specific immunoglobulin E (IgE)/total IgE compared with specific IgE (sIgE) alone in predicting symptomatic food allergy.

Methods: We retrospectively analysed 992 controlled oral food challenges performed in 501 children (median age 13 months). The ratio of sIgE/total IgE was calculated and tested for correlation with the outcome of food challenges. Receiver operator characteristics (ROC)-curves were performed; predicted probabilities and predictive decision points were calculated.

Results: A significant correlation was found between the ratio and the outcome of food challenges for cow's milk (CM), hen's egg (HE), and wheat, but not for soy. The ROC and predicted probability curves as well as sensitivity and specificity of the decision points of the ratio were similar to those of sIgE levels for CM, HE and wheat.

Conclusion: In view of the greater effort needed to determine the ratio, without benefit compared with the sIgE alone, the calculation of the ratio of sIgE/total IgE for diagnosing symptomatic food allergy offers no advantage for CM, HE, wheat or soy. For the majority of cases controlled oral food challenges still remain the method of choice.

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Key words: children; double-blind, placebo-controlled food challenges; food allergy; food challenge; ratio; specific immunoglobulin E; total immunoglobulin E.

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The increasing prevalence of food allergy in children (1, 2) and growing public awareness have led to an increase in the demand for evaluation of suspected food allergy. While double-blind, placebo-controlled food challenges (DBPCFC) still represent the gold standard for the diagnosis of food allergy, they are time-consuming, expensive and troublesome for the patient, involving the risk of severe systemic reactions. An *in vitro* test that could accurately diagnose food allergy would be of great value.

In recent years, efforts have been made to find diagnostic tests to predict the outcome of oral food challenges. The skin prick test (SPT) (3, 4), the atopy patch test (APT) (5–7) and the determination of food-specific immunoglobulin E (IgE)-antibodies (8–12), are important tools in the diagnostic work-up of food allergy, and also in primary care (13, 14).

Abbreviations: AD, atopic dermatitis; APT, atopy patch test; AUC, area under the curve; CM, cow's milk; DBPCFC, double-blind, placebo-controlled food challenges; HE, hen's egg; IgE, immunoglobulin E antibodies; NPV, negative predictive value; PPV, positive predictive value; Ratio, ratio of specific IgE/total IgE; ROC, receiver operator characteristics; sIgE, specific IgE; SPT, skin prick test.

However, they still cannot render oral food challenges unnecessary in most cases.

Diagnostic decision points for specific serum IgE have been established to predict symptomatic food allergy (8–12). While the specificity of these decision points is good, sensitivity is unsatisfactory. Considering that food allergy is often the beginning of an 'allergic march' and is associated with other atopic diseases in many cases, one may take the total IgE into account and should interpret specific IgE (sIgE) levels differently in patients with high total IgE levels compared to those with low levels. This may especially be true for children with atopic dermatitis (AD), who frequently show very high total IgE levels and numerous sensitizations, often without clinical relevance. We therefore hypothesized that a higher ratio of sIgE/total IgE may result in a higher probability of symptomatic food allergy.

Methods

Study population

We retrospectively studied 501 children consecutively referred to the Department of Pediatric Pneumology and Immunology at Children's

Hospital Charité for evaluation of suspected food allergy. Patients' ages ranged from 3 months to 16 years of age (median: 13 months) and the majority were boys (59.5%). A total of 440 patients (87.8%) had a history of AD as defined by the criteria of Sampson (15) and Seymour et al. (16), modified from Hanifin and Rajka (17). About 204 of these patients had mild AD (SCORAD 1–24 points), 116 moderate AD (25–49 points), 56 severe AD (≥ 50 points), and 64 patients had no current AD at the time of oral food challenge. About 67 children had a diagnosis of asthma, 29 had at least one episode of obstructive bronchitis. Furthermore, 46 children suffered from allergic rhinoconjunctivitis. The diagnosis of food allergy was based on the outcome of controlled oral food challenges.

Scoring of atopic dermatitis

As prescribed previously, severity of AD was scored according to the SCORAD score (18–20) with assessment of topography items, intensity criteria and subjective or reported parameters. The maximum possible score was 103 points.

Determination of IgE antibodies

Blood was drawn prior to the oral challenge. Patient serum was analysed for concentrations of total IgE and sIgE to cow's milk (CM), hen's egg (HE), wheat, and soy, using the Pharmacia CAP-System FEIA® (Pharmacia-Diagnostics, Uppsala, Sweden). The lower detection limit of the CAP-System was 0.35 kU/l. If food-specific IgE levels were above 100 kU/l, the serum was diluted and measured.

Oral food challenges

Oral challenges were performed as a result of a suggestive medical history, and/or positive SPT, and/or sIgE levels above 0.35 kU/l. For this study, we analysed the four most common food allergens in European children: CM, HE, wheat and soy. The majority, 728 of 992 (73.4%) of challenges, was performed as DBPCFC. Open challenges were allowed in children younger than 1 year of age who had a clear history of immediate type reactions ($n = 264$, 26.6%). The clinical dietician performed the randomization and preparation of the challenges. Briefly, successive doses (0.1, 0.3, 1.0, 3.0, 10.0, 30.0 and 100.0 ml) of fresh pasteurized CM containing 3.5% fat, of soymilk or placebo (Neocate, SHS, Liverpool, UK) were administered (21–23). Wheat (gluten) powder (Kröner, Ibbenbüren, Germany) and raw HE (white and yolk) were given in successive doses reaching a total amount of 5 g for wheat (gluten) protein and one complete egg, respectively.

Doses were increased every 30 min. Full emergency equipment was at hand including adrenaline, glucocorticosteroids, antihistamines and β -agonists. The time interval between challenges was 48 h to evaluate late reactions as well. Children receiving an antihistamine were advised to avoid it at least 72 h prior to provocation. Topical steroids were allowed twice daily at a concentration of 1% hydrocortisone or 0.01% betamethasone. For children with AD, challenges were only started when a stable clinical condition was reached. Children had to be free of acute symptoms of asthma or allergic rhinoconjunctivitis. Prior to provocation, the patients had to have been on elimination diet for the tested allergen for at least 1 week.

The provocation was stopped if clinical symptoms were observed or the highest dose was reached. The food challenges were scored as positive by a paediatric allergy specialist if one or more of the following objective clinical reactions were noted: urticaria, angio-oedema, wheezing, vomiting, diarrhoea, shock or exacerbation of eczema (at least a 10-point increase in SCORAD score) (24).

Symptoms within 120 min after administering the last dose were defined as early reaction, symptoms occurring after more than 2 h as late reaction.

Statistics

For the statistical analysis we used spss for Windows (version 11.5). The ratio of sIgE/total IgE was calculated if specific and total IgE were 0.35 kU/l or higher. Mann–Whitney *U*-test was used to check for statistical correlation between outcome of oral food challenge and the ratio of sIgE/total IgE. Comparisons were considered significant at $P < 0.05$. The receiver operator characteristics (ROC)-curves were performed and area under the curve (*AUC*) was calculated to compare the accuracy of the test for sIgE alone and for the ratio of sIgE/total IgE. In addition, we calculated probabilities for the outcome of oral food challenge by means of sIgE as well as by the ratio of sIgE/total IgE using the logistic regression resulting in predictive decision points (8, 9).

Results

A total of 992 controlled oral food challenges were analysed in 501 children. With CM, 196 of 398 (49.2%) challenges were assessed as positive: 139 early, 25 late and 32 combined early and late reactions. In challenges with HE, 151 of 227 (66.5%) were positive: 118 early, six late and 27 combined reactions. About 63 of 178 (35.4%) provocations with wheat were assessed as positive (30 early, 17 late and 16 reactions). Of the soy challenges, 35 of 189 (18.5%) was assessed as positive (11 early, 15 late and nine combined reactions).

Total IgE ranged from 0.3 to 13 525.0 kU/l (median: 94.3). The ratio of food-specific IgE/total IgE ranged from 0 to 91.2% (median: 0.3) for CM, 69.4% (median: 1.7) for HE, 70.7 (median: 0) for wheat and 15.0% (median: 0) for soy. Mann–Whitney *U*-test was performed to examine whether there is a significant correlation between the ratio and the outcome of oral food challenge. This could be confirmed for CM ($P < 0.001$), HE ($P < 0.001$) and wheat ($P = 0.001$) but not for soy (NS).

Figure 1 shows the graphic representation of sensitivity and specificity obtained by calculating ROC-curves for all four allergens: food-specific IgE alone and ratio of specific/total IgE, respectively. The *AUC* for CM was 0.79 for the ratio, and 0.76 for sIgE alone. For HE, the *AUC* for the ratio was 0.86, and 0.88 for sIgE. The *AUC* was lower for wheat, with 0.66 for the ratio, and 0.66 for sIgE; and lowest for soy, 0.58 (ratio) and 0.64 (sIgE).

The predicted probabilities for a symptomatic food allergy at a given ratio of sIgE/total IgE calculated by a logistic regression model are shown in Fig. 2. The curves for milk, egg and wheat were almost identical for the ratio and sIgE alone.

Choosing a 95% predicted probability as proposed in the literature resulted in a decision point for the ratio of 19.1% for HE only (Fig. 2). About 15 of 151 positive

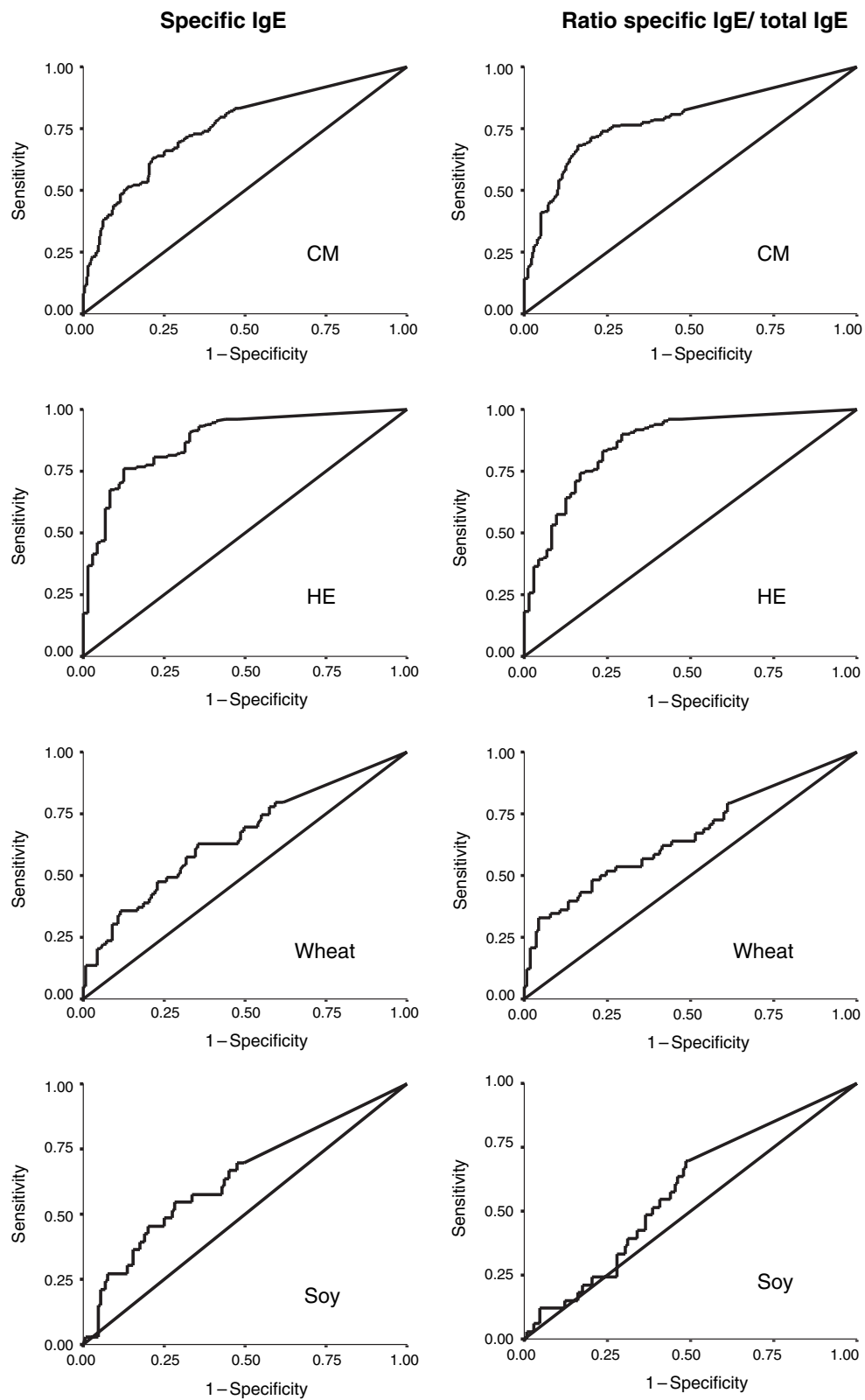


Figure 1. Receiver operator characteristics (ROC)-curves for cow's milk (CM), hen's egg (HE), wheat and soy: specific immunoglobulin E (IgE) levels and the ratio of specific IgE/total IgE, respectively.

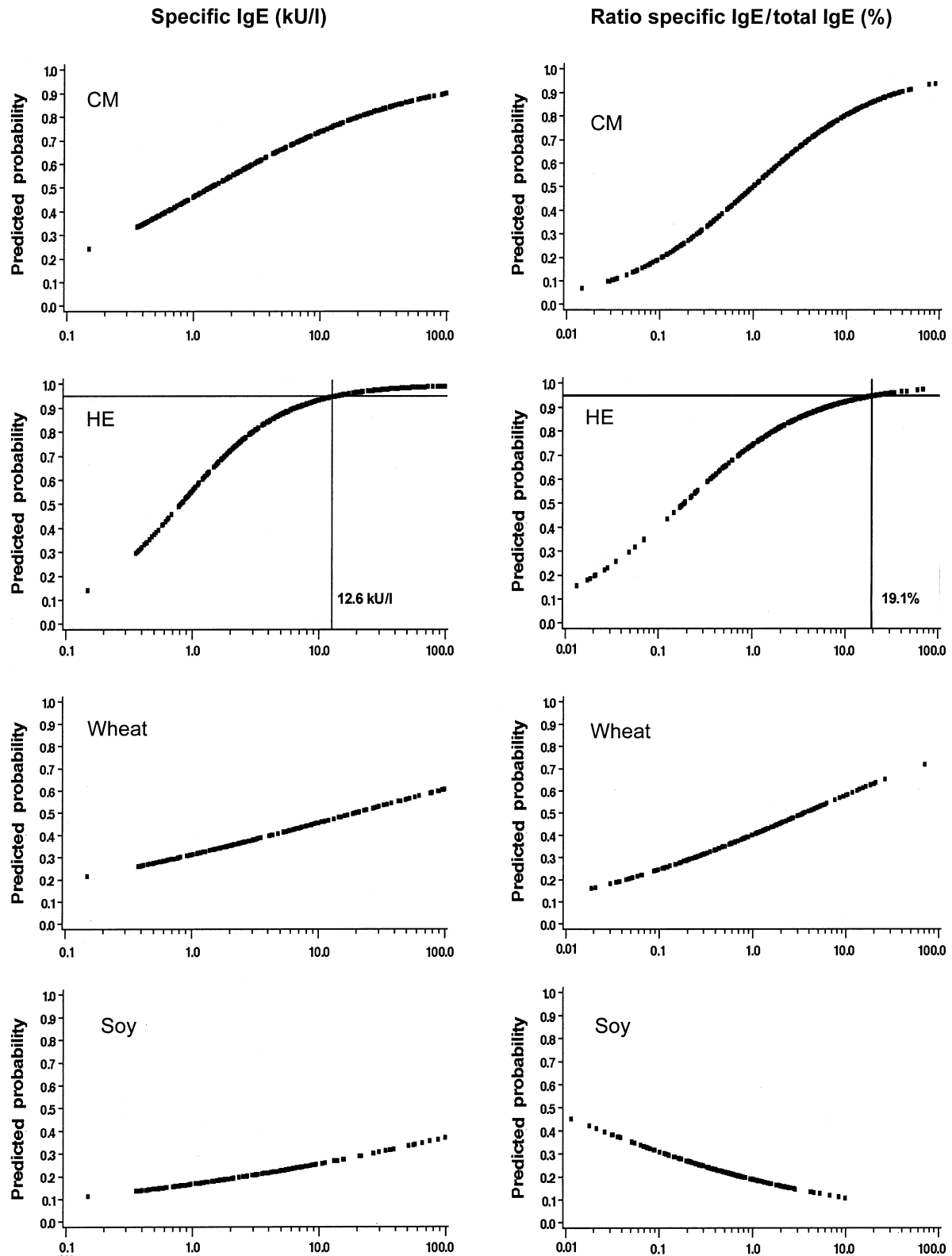


Figure 2. Predictive probabilities for a positive food challenge in relation to specific immunoglobulin E (sIgE) levels (kU/l) and to the ratio of sIgE/total IgE (%).

challenges with HE (10%) fulfilled this criterion. While sensitivity and negative predictive value (NPV) were low (10.0 and 35.7%), specificity (100%) as well as positive predictive value (PPV) (100%) was high. No 95% predicted probability could be reached for the remaining allergens CM, wheat and soy. A predicted probability of 99% could not be reached for any of the four allergens, while calculating 90% predicted probabilities resulted in decision points for HE (5.9%) and for CM (33.6%).

Discussion

Our investigation shows that the ratio of sIgE/total IgE is significantly correlated with the outcome of oral food challenges for CM, HE, and wheat. For these three allergens a higher ratio correlates with an increased probability of symptomatic food allergy. There was no significant correlation for soy. However, our data also demonstrates that the ratio is not superior to the use of sIgE levels alone.

In vitro tests to predict the outcome of oral food challenge would be of tremendous help in daily practice. In recent years, several studies have shown the diagnostic value of food-specific IgE levels in diagnosing symptomatic food allergy. Sampson and Ho (8), followed by several other study groups (9–11) established 95% predictive decision points and suggested that an oral food challenge should not be performed in patients with sIgE levels in serum reaching or exceeding these values. However, the established levels vary widely between the study groups. In addition, due to the low sensitivity of these decision points they should not be used for excluding a symptomatic food allergy. Therefore, the determination of the sIgE level can render oral provocations dispensable only in certain cases, and food challenges are still necessary in the majority of the patients. Especially in children with AD, a patient group, which typically has the most elevated IgE levels (25), the interpretation of the sIgE level is often very difficult.

For this reason, it seemed interesting to take the total IgE into account and to calculate the ratio of sIgE/total IgE. However, as shown by *AUC*-values of the ROC-curves (Fig. 1), the accuracy of the ratio as a diagnostic test to distinguish between symptomatic and nonsymp-

tomatic patients is not satisfactory and at least is not beneficial compared with the sIgE levels alone. Calculating decision points for the ratio representing a 95% predicted probability for a positive oral challenge with all four foods did not improve the specificity and sensitivity significantly compared with sIgE levels alone. Only for HE, a 95% predicted probability could be calculated for both sIgE and the ratio. However, these 'cut off levels' involve a low sensitivity, and the ratio does not improve the accuracy in diagnosing symptomatic food allergy compared with the sIgE level alone.

Using 95% predictive decision points, 5% of children might be subjected to unnecessary dietary restrictions. To avoid this, we suggest increasing the predicted probability to a level of 99%. Going through an oral challenge under strict medical surveillance seems to be less harmful than an elimination of food such as CM, HE, wheat, and soy. For the ratio, however, 99% predicted probabilities could not be reached for all four allergens.

Our analysis was retrospective, but this seems not to present a bias, as shown by Sampson (9) validating retrospectively established decision points for the sIgE level with prospectively analysed data. Therefore, compared with other studies on diagnostic decision points, a larger number of patients could be included in our study.

In conclusion, for diagnosing symptomatic food allergy of CM, HE, wheat or soy, the determination of the ratio of food-specific IgE/total IgE gives similar results to the determination of food-specific IgE alone. Considering the greater effort necessary for calculating the ratio, there is no benefit compared with the sIgE. In the majority of cases controlled oral food challenges still remain the method of choice.

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