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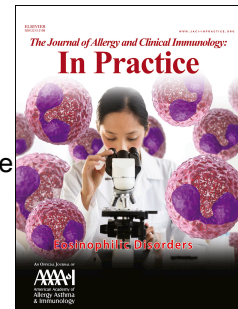
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Diagnosis of Sesame Allergy: Analysis of Current Practice and Exploration of Sesame Component Sensitization

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Abstract

BACKGROUND: Sesame is an allergen of increasing importance.

OBJECTIVE: We sought to characterize the outcomes of oral food challenges (OFCs) to sesame and evaluate the diagnostic accuracy of skin prick testing (SPT), sesame and Ses i 1-specific IgE (sIgE).

METHODS: We reviewed sesame OFCs performed at the Mount Sinai pediatric allergy clinic between January 2010 and April 2018. We assessed the accuracy of diagnostic tests by calculating the area under the curve (AUC) of the receiver operating characteristic (ROC) curves. Association between OFC outcome and sesame sensitization was analyzed using a logistic regression, which was then used to estimate the 95% positive predictive value (PPV) of these tests.

RESULTS: We identified 341 patients (69% male, mean age 7.7 years) who underwent sesame OFC. Among 106 (31%) positive OFCs, the median cumulative eliciting dose was 500 mg sesame protein ($\frac{1}{2}$ teaspoon tahini). Sesame SPT wheal ≥ 6 mm had sensitivity 54.1% and specificity 87.8%; AUC 0.756 [95% CI 0.699 to 0.814]. SPT wheal size ≥ 14 mm had 95% PPV. Sesame-sIgE level did not correlate with OFC outcome. Ses i - sIgE levels were analyzed in 30 patients using ISAC microarray and were significantly associated with OFC outcome (AUC: 0.715 [95% CI 0.541 to 0.890]). Ses i 1-sIgE ≥ 0.3 ISU had sensitivity 58.3% and specificity 83.3%.

CONCLUSIONS: This is the largest study of sesame allergy to date. Sesame SPT is a more accurate predictor of sesame allergy compared to sesame sIgE. Ses i 1-sIgE appears promising but requires further study regarding diagnostic accuracy.

Abstract word count: 247

1. What is already known about this topic?

Sesame is a food allergen of increasing importance, although the relevant diagnostic decision points have not been firmly established for skin prick testing, sesame-specific IgE or sesame component Ses i 1.

2. What does this article add to our knowledge?

Sesame skin prick test is a more accurate predictor of sesame allergy compared to sesame specific IgE. Ses i 1-specific IgE seems to be a good candidate but further studies are warranted.

3. How does this study impact current management guidelines?

Sesame oral food challenge (OFC) could be safely offered to children sensitized to sesame without prior reactions. A skin prick test wheal ≤ 6 mm threshold is proposed as a clinical decision point for offering sesame-OFC.

Key words: food allergy, sesame, skin prick test, serum-specific IgE, Ses i 1, oral food challenge, predictive value, diagnosis, sesame IgE

Abbreviations:

AUC: Area Under the Curve

CI: Confidence Interval

83	IQR:	InterQuartile Range
84	ISAC:	ImmunoSolid phase Allergen Chip
85	ISU:	ISAC Standardized Units
86	NPV:	Negative Predictive Value
87	OFC:	Oral Food Challenge
88	PPV:	Positive Predictive Value
89	ROC:	Receiver Operating Characteristics
90	sIgE:	Serum Allergen-specific Immunoglobulin E
91	SPT:	Skin Prick Test

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INTRODUCTION

Current estimates suggest that food allergies affect 7.6% of children in the United States.¹ Seeds are among the small number of foods responsible for the majority of reactions.^{2,3} Sesame (*Sesamum indicum*) is the most common seed allergen.⁴ The prevalence of sesame allergy varies according to geographic location. In the Middle East, where sesame seeds are widely consumed, sesame is one of the most common food allergens.^{5,6} Due to migration and globalization, consumption of sesame in Western countries has increased.⁷ Sesame allergy has been increasingly self-reported, with an estimated 0.1-0.2% prevalence in North America.^{1,8-10} In Australia, food challenge-proven sesame allergy has been reported in 0.8% of 12 month-old infants from an unselected cohort.^{11,12}

Sesame has the potential to cause severe allergic reactions. In France, sesame has been identified as a trigger for 3% of cases of food-induced anaphylaxis.¹³ Pediatric Canadian study exposed the high risk of accidental exposure, potentially leading to anaphylaxis, contributing to sesame being added to the Canadian food allergens labelling list¹⁴. The U.S. Food and Drug Administration is considering including sesame among the major food allergens that have to be disclosed on a food label.¹⁵ Sesame allergy is usually life-long, with tolerance developing in approximately 20-34% of patients.^{16,17}

An oral food challenge (OFC) is the gold standard for the diagnosis of food allergy.^{18,19} However, OFCs are resource-intensive, time-consuming, and carry a risk of anaphylaxis,^{20,21} justifying the importance for alternative diagnostic studies. Serum levels of food-specific IgE (sIgE) antibodies and skin prick tests (SPTs) are routinely used for food allergy diagnosis. A 95% positive predictive value (PPV) for these tests is an accepted surrogate to the OFC in clinical practice.²² Another approach is based on component-resolved diagnosis (CRD), which is promising especially for cross-reactive food and pollen allergens.³ Seven sesame allergen components,

including the major allergen 2S albumin Ses i 1,²³ have been registered by the WHO/IUIS Allergen Nomenclature Subcommittee.²⁴⁻²⁶ Data regarding the diagnostic utility of these components are inconclusive, particularly because of the absence of clear thresholds.²⁷ Two Japanese studies reported that Ses i 1-sIgE had a superior diagnostic accuracy versus whole sesame-sIgE and Ses i 2-sIgE.^{28,29}

We sought to determine whether sesame-sIgE and SPT accurately predict sesame OFC outcome in the American children. In addition, we aimed to evaluate the diagnostic accuracy of Ses i 1-sIgE in a subgroup analysis.

METHODS

Study design

The study was approved by the Institutional Review Board. We reviewed all sesame OFCs from January 2010 to April 2018 at the Elliot and Roslyn Jaffe Food Allergy Institute at the Icahn School of Medicine at Mount Sinai in New York, a pediatric, university-based outpatient practice. Patients with suspected sesame allergy were referred for open OFC by Mount Sinai's allergists based on clinical criteria. These patients avoided sesame in the diet, had evidence of sesame-IgE sensitization. Allergic reaction to sesame within the past 2 years was usually a contraindication to the OFC. The OFCs were performed per standard protocol,^{18,30} usually doubling doses every 15 minutes until an age-appropriate serving was ingested, approximately 18 g of sesame seeds or 6 teaspoons of tahini paste for patients older than 3 years of age. The inclusion criterion was a conclusive sesame-OFC, irrespective of a reaction history, sesame SPT and sIgE results. We analyzed demographic, clinical, and laboratory information, including reason for sesame avoidance, prior sesame allergic reactions, co-allergies to peanut, tree nuts, and other seeds (assessed by a clear history of reaction or a positive OFC). The details of the sesame-OFC including dosing, any reported symptoms or signs of a reaction, treatment, and the OFC outcome were recorded. The OFC outcome was reported as negative (passed), positive (failed), or inconclusive. OFCs were deemed inconclusive if the patient failed to ingest a sufficient quantity of sesame, had confounding concurrent symptoms, or reported a delayed reaction that did not meet the positive challenge criteria. The accepted definition of anaphylaxis was used to assess severe reactions.³¹⁻³³

SPTs were performed using sesame commercial extract (Greer Laboratories, Inc, Lenoir, NC, USA) and bifurcated needles (Hollister-Stier Labs) on patients' forearm. Negative (50% glycerin-saline) and positive (histamine) controls were performed concurrently. The results were read at 10-15 minutes; wheal and erythema diameters were measured and means calculated. A wheal of ≥ 3 mm greater than negative control was considered a positive test. Serum sesame-sIgE antibodies were analyzed by using the ImmunoCAP (Thermo Fisher Scientific, Waltham, MA, USA). A subset of patients underwent additional Immuno Solid-phase Allergen Chip (ISAC®) microarray (ImmunoCAP, Thermo Fisher Scientific, Uppsala, Sweden) testing prior or immediately after sesame-OFC. These patients participated in a study examining the utility of the ISAC microarray from June 2011 to June 2013.³⁴ For that patient subset, testing included sesame component Ses i 1-sIgE. The lower detection limit of the assay was 0.35 kU_A/L for sesame-sIgE and 0.3 ISAC Standardized Units (ISU) for Ses i 1-sIgE; sesame IgE value ≥ 0.35 kU_A/L and Ses i 1 value ≥ 0.3 ISU were considered positive. The ImmunoCAP ISAC® microarray test was provided by Thermo Fisher Scientific (Waltham, MA, USA), however, the authors independently performed and are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents.

Statistical Methods

The diagnostic accuracy of SPT, sesame-sIgE, and Ses i 1-sIgE were assessed using receiver operating characteristic (ROC) curves. The optimal cut-off maximizes both sensitivity and specificity ratio on the ROC curve. The area under each ROC curve (AUC) was calculated to estimate the accuracy of each of the three tests. DeLong's test was used to compare AUCs. Logistic regression models were fit to estimate associations between the outcome "sesame allergy" (e.g., positive vs. negative sesame OFC), as to the IgE-sensitization (SPT wheal size

diameter or specific IgE level). Fitted predicted probability curves were plotted using the results from logistic regression. Modeled PPVs deriving from the logistic regression models were used to estimate thresholds of interest for SPT and sIgE and their 95% confidence intervals (CI).

Continuous variables were reported as mean $\pm$ standard deviation (SD) or median $\pm$ interquartile range (IQR) depending upon normality of distribution. Two-sample t-tests were used for comparing normally distributed variables whereas non-parametric Mann–Whitney *U*-tests were used to compare non-normally distributed variables. Comparison between groups was performed for categorical variables using Pearson’s Chi-Square test if the conditions were met (i.e. > 5 observations per group) ; if not, Fisher’s-exact test was used. Variables associated to OFC outcome with a p-value < 0.20 in univariate analyses were included in a multivariate logistic regression model. All analyses were two-sided, and a p-value ≤ 0.05 was considered statistically significant. The outcome of all analyses was the sesame OFC result (positive or negative). All analyses were performed with RStudio (2016): Integrated development environment for R (Version 1.1.456) (Boston, MA).

RESULTS

In total, 367 sesame-OFCs were performed. We excluded 26 (7%) inconclusive challenges from the study. Among 341 conclusive sesame-OFCs (age range 8 months to 22 years), 106 (31.1%) were positive and 235 (68.9%) were negative. The demographic characteristics of each group along with univariate and multivariate analyses are presented in Table I.

Prior reactions to sesame ($X^2= 18.61$; $P<0.0001$) and anaphylaxis to sesame ($P<0.01$; Fisher's exact test) were significantly associated with positive OFCs. There was no difference regarding concomitant peanut, tree nut, or seed allergies (supplemental Table E1). The most common symptoms observed during the sesame-OFC were cutaneous (86%), followed by oropharyngeal/naso-ocular (56%), gastrointestinal (37%), and lower respiratory (15%). No biphasic reactions were reported.

The sesame-OFC was administered in 4 forms: tahini (78%), sesame seeds (22%), hummus (2%), and sesame butter (0.3%). The choice of sesame form for the OFC was driven by the patient and family preference. There was no significant difference in the OFC outcome according to the ingested form ($X^2= 1.76$; $P=0.18$ for tahini and $X^2= 1.94$; $P=0.16$ for sesame seeds). The median cumulative eliciting dose to which patients reacted was 500 mg sesame protein (equivalent to $\frac{1}{2}$ teaspoon of tahini; 2900 mg or 1 teaspoon of sesame seeds) [IQR: 250 to 1500 mg sesame protein, respectively 1455 mg to 8735 mg of sesame seeds)].

Patients with prior reactions to sesame

The majority of patients ($n=257$; 75.3%) had no prior reactions to sesame and were avoiding sesame due to positive testing found during the evaluation of a patient with another food allergy (mainly peanut allergy); 77% ($n=198$) of them never ingested sesame prior to the OFC.

Eighty-four (24.6%) patients reported a prior reaction to sesame (more than 2 years prior to OFC); of these, 11 (13.1%) had been treated with epinephrine but none were severe.

Co-morbid asthma ($X^2 = 10.21$; $P < 0.01$) and allergic rhinitis ($X^2 = 5.86$; $P < 0.05$) were more common in patients with a history of reaction to sesame. No differences were observed regarding atopic dermatitis, peanut, tree nut or seed co-allergies (data not shown).

Half of the patients with a prior reaction to sesame reacted during sesame-OFC ($n = 42$; 50%), compared to 25% patients without prior sesame reactions ($X^2 = 18.61$; $P < 0.0001$). There was no significant difference in the symptoms and the treatments administered during the OFC between these two groups (data not shown).

Anaphylaxis during sesame OFC

Twenty-three (22% of positive OFCs; 7% of total challenges) patients had an anaphylaxis. Of these, 21 (20% of positive OFCs; 6% of total challenges) were treated with epinephrine; one dose in 19 patients and two doses in 2 patients. Individual clinical and immunologic characteristics are summarized in supplemental Table E2. There was no association between anaphylaxis and patient age ($t = -0.57$; $P = 0.57$) or cumulative eliciting dose, regardless of patient age ($t = 0.58$; $P = 0.57$). We observed no significant differences in SPT wheal size between patients with anaphylactic and mild reactions ($W = 858$; $P = 0.46$). However, sesame-sIgE levels were significantly higher among patients with anaphylaxis [median: 3.88 kU_A/L (IQR: 1.22 - 7.99 kU_A/L)] compared to patients with milder reactions [median: 1.61 kU_A/L (IQR: 0.77 - 3.98 kU_A/L)] ($W = 571$, $P < 0.01$).

Skin prick testing to sesame

SPTs were recorded for 339 (99.4%) patients; of those, 100 (29.5%) patients had negative sesame SPTs. The median SPT wheal size was larger in the group with positive vs. negative

OFCs at 6 mm (IQR: 4 – 7 mm) and 3 mm (IQR: 0 – 5mm) respectively ($W=6,014$; $P<0.001$). Among 100 patients with a negative SPT (0mm), 12 (12%) had a positive OFC; 3 (25%) were treated with epinephrine (see supplemental Table E3). The relationship between sensitivity and specificity is presented as a ROC curve in Fig 1. The area under the curve (AUC) was estimated as 0.756 (95% CI; 0.699 - 0.814). For an average patient, a 1 mm increase in SPT wheal size was associated with significantly greater odds of a positive OFC outcome ($P<0.001$; *adjusted odds-ratio*, 1.47 [95% CI, 1.33-1.66]). Several SPT cutoffs were assessed along with sensitivity, specificity, and positive and negative predictive value (PPV and NPV) in Table II. A SPT wheal size ≥ 6 mm demonstrated a specificity of 87% and was the optimal cut-off in the ROC curve. The 95% PPV value was not observed in this population. However, this decision point was estimated to be ≥ 14 mm (95% CI, 12.5 – 17.5mm) using the modeled probability predicted curve and a 50% PPV was estimated to be ≥ 6 mm (95% CI, 6 – 8mm) (Fig 2-A). Seven patients (age range: 6.7 – 16.7 years) had a positive OFC with subjective symptoms only but all had positive testing [SPT range: 0 – 9mm; sesame-sIgE range: 0.94 – >100 kU_A/L]. Excluding their results from the AUC and logistic regression analyses did not affect the results, and the 95% PPV SPT threshold remained unchanged.

Serum sesame-specific IgE testing

Sesame-sIgE values were documented for 332 (97.3%) patients. Sesame-sIgE levels were not associated with the outcome of the OFC ($W=11,896$; $P=0.92$). The sesame-sIgE was higher in patients with passed sesame OFCs [median of 2.15 kU_A/L (interquartile range, IQR: 0.25-4.96kU_A/L)] vs. failed OFCs [1.88 kU_A/L (IQR: 0.94-4.67kU_A/L)]. Undetectable sesame-sIgE levels were not predictive of a negative OFC. Among 40 patients with sesame-sIgE level below 0.35 kU_A/L, 14 (35%) failed the OFC. One (2.5%) patient was treated with epinephrine

(supplemental Table E4). AUC did not reach 0.5 cut-off (AUC=0.497; 95% CI, 0.429 – 0.564). The AUCs' comparison for diagnostic performance favored sesame SPT over sesame-sIgE ($D=5.57$; $P<0.001$). The 95% PPV for sesame-sIgE could not be calculated (see Fig 2-B). Several cutoffs are presented along with sensitivity, specificity, PPV, and NPV values in Table III. The sesame-sIgE and SPT were double negative before OFC in 14 (4.1%) patients; 2 (14.3%) failed OFC with mild objective symptoms.

Ses i 1-specific IgE

Sesame component Ses i 1-sIgE was available for 30 (8.8%) patients whose characteristics are presented in supplemental Table E5. Of those, 12 (40%) reacted during the OFC. Twenty (67%) patients had an undetectable Ses i 1-sIgE level. Five (25%) patients had a positive OFC despite an undetectable Ses i 1-sIgE, and 1 (5%) patient had a negative sesame SPT and an undetectable sesame-sIgE. A threshold ≥ 0.3 ISU had a specificity of 83.3%, a sensitivity of 58.3%, PPV of 70.0%, and NPV of 75.0%. The median values and AUC for the three tests (SPT, sesame-sIgE and Ses i 1-sIgE) from this subgroup population are presented in Table IV. Ses i 1-sIgE was significantly associated with the OFC outcome ($W=61.5$; $P<0.05$), unlike SPT ($W=77.5$; $P=0.20$) or sIgE ($W=101$; $P=0.98$) in this subset. There was no significant difference between the three AUCs (Fig 3). Ses i 1-sIgE cutoffs with their sensitivity, specificity, PPV and NPV values are presented in supplemental Table E6.

DISCUSSION

We report the results of the largest study to date exploring the diagnostic testing for sesame allergy. As sesame has emerged as one of the major food allergens capable of triggering anaphylaxis and causing persistent allergy, it is important to gain a better understanding of the diagnostic utility/accuracy of the available diagnostic tests. While OFCs remain the gold diagnostic standard for food allergy, the availability of OFCs is limited, in part due to physicians' and patients' reluctance to pursue a labor-intensive procedure with a risk of anaphylaxis. Therefore, so-called diagnostic decision points that estimate the risk of a positive OFC are very useful for risk stratification when evaluating candidates for an OFC in practice. However, the utility of the diagnostic decision points is limited because they tend to be specific for the patient population. In our study, sesame SPT had a significantly better diagnostic accuracy than sesame-sIgE. Based on the probability curves, sesame SPT wheal size of 14 mm or greater has a 95% PPV for sesame allergy, and a 6 mm SPT threshold had 53.8% sensitivity and 87.1% specificity. In contrast, sesame-sIgE was a poor predictor of allergy, AUC of 0.497. The predictive probability curve of the latter could not reach the 95% PPV decision point. In the Ses i 1-sIgE subgroup analyses, the Ses i 1-sIgE had a better diagnostic accuracy in comparison to both sesame-SPT and sesame-sIgE, however without reaching a statistical significance. This might have been due to a small number of patients with available Ses i 1-sIgE levels, warranting further exploration of sesame components. The proportion of patients who failed the OFC despite a negative testing was higher with sesame-sIgE (35%), followed by Ses i 1-sIgE (25%) in the subgroup analysis and sesame-SPT (12%). The proportion of patients who passed the OFC despite positive testing was high, reaching 69%, 61% and 30% respectively with sesame-sIgE, sesame-SPT and Ses i 1-sIgE.

The majority of sesame-OFC offered on the basis of SPT and sIgE were negative but the number of reactions, including anaphylaxis, was not inconsequential. Of these OFCs, 6.2% reactions were treated with epinephrine, comparable to the average rate (under 10%) of reactions treated with epinephrine during OFCs in children.¹⁹ The median cumulative eliciting dose of sesame protein was 500 mg (equivalent to ½ a teaspoon of tahini and 2.9 g of sesame seeds). There was no correlation between cumulative eliciting dose and reaction severity. Among patients with prior reactions to sesame, 50% did not react during the OFC, suggesting, that in our population, the rate of resolution of sesame allergy might be higher than previously reported^{16,17}. However, a potential recruitment bias might skew this result. In addition, the majority of patients with a prior history of anaphylaxis to sesame reacted during sesame OFC (9/12, 75%), suggesting caution when offering sesame OFC to such patients.

Our 95% PPV decision point for sesame SPT was higher than the 8mm wheal size previously reported by Peters et al³⁵ in the Australian HealthNuts study cohort with infants from 11 to 15 months old. Sesame SPT wheal of 3 mm had a lower PPV among our patients (38%) compared to Peter's younger population (58%). Permaul et al found similar results to our study with children aged 2 to 12 for the same 3 mm threshold (31% PPV and 88% NPV) but without being able to reach a 95% PPV.³⁶ Nevertheless, we noted that a negative SPT did not exclude sesame allergy or anaphylaxis. Our results support the previous findings that sesame-sIgE has sub-optimal diagnostic performance.²⁷ In our study, an undetectable sesame-sIgE did not exclude sesame allergy, in contrast to previously reports.^{37,38} In the HealthNuts study, the highest PPV estimated was 86% for sesame sIgE threshold of 50 kU_A/L. Permaul et al reported that 29% of their sesame allergic patients had an undetectable sesame-sIgE level, with a low overall accuracy

(AUC 0.56). The positive sIgE threshold detection (≥ 0.35 kU_A/L) had 71% sensitivity and 31% specificity (22% PPV, 80% NPV).³⁶ The differences between our results and previous findings could be explained by patients' age, different geographic location²⁷ and other characteristics of the study population. PPV and NPV are dependent on the disease prevalence in a specific population. Specific decision points determined in one center may differ from another center.

Component-resolved diagnostic tests are valuable tools in the diagnosis for allergy to peanut, tree nuts, and some other foods.³ Our results support the previous findings regarding the utility of Ses i 1-sIgE. In an *in vitro* IgE performance study, the experimental ImmunoCAP rSes i 1-sIgE had the best diagnostic accuracy with an AUC of 0.896 compared to the major sesame experimental components and the commercially available sesame extracts.²⁸ However, we used a different assay in our study: ISAC microarray, making it impossible to compare the thresholds.

A positive OFC in the setting of negative laboratory testing might be explained by absent relevant major sesame allergens in the currently available tests, which are based on the aqueous sesame extracts. Commercial extracts used for SPT are processed using a de-fatting procedure, thus these extracts have a low content of fat-soluble allergenic proteins such as oleosins.³⁹ Likewise, processing methods for whole sesame ImmunoCAP result in under-representation of the sesame major allergens or under-recognition of the epitopes altered by the coupling procedure.²⁶ Oleosins have been identified as allergens in sesame, peanut (Ara h 10 and Ara h 11) and hazelnut (Cor a 12 and Cor a 13). Sesame oleosins (Ses i 4 and Ses i 5) induce reactions in patients with negative screening tests. Leduc et al presented the results of 32 OFC-proven sesame allergic patients in a French study, including 17 children (age range: 3-18 years). Negative SPT and undetectable sesame-sIgE levels were reported for 82% and 18% children, however, all had positive immunoblot toward sesame oleosins.²⁶ More recently, Barbarroja-Escuedo et al described 10 Spanish sesame-allergic adults with 100% negative sesame extract SPTs, 80%

undetectable sesame-sIgE, and 10% negative sesame seed skin prick-prick testing. All these patients had positive immunoblot toward sesame oleosins.⁴⁰ Anaphylactic reactions were observed in both studies, in 31% of the pediatric patients²⁶ and in 80% of the adults.⁴⁰ Teodorowicz et al identified oleosins (Ses i 4 and/or Ses i 5) as the major allergen in 5 Dutch patients with sesame anaphylaxis.⁴¹

Patients sensitized but tolerant to sesame represented 57% of our population. In a study by Maruyama et al, nearly all the patients were sensitized to the other seed storage proteins 7S globulins (vicillin, Ses i 3) and 11S globulins (legumins, Ses i 6 and Ses i 7) irrespective of their sesame allergy status. These proteins have a high homology with peanut and tree nut proteins; vicillins: peanut Ara h 1, cashew Ana o 1, walnut Jug r 6, and legumins: peanut Ara h 3, cashew Ana o 2 or walnut Jug r 4⁴². These results could explain high (62%) rate of co-sensitization to peanut and/or tree nuts in our patient population (see supplemental Table E1). These results also suggest that sesame allergy tends to be over-diagnosed due to cross-sensitization with peanut and/or tree nuts. Sub-optimal specificity of the currently available diagnostic tests leads to unnecessary sesame avoidance and a negative effect on quality of life. It is also possible that avoidance of sesame in the diet could lead to development of symptomatic sesame allergy due to exposure via non-ingestion routes, especially in children with atopic dermatitis, as has been observed for peanut⁴³ and egg.⁴⁴

Our study has several limitations. It is a retrospective review of sesame OFCs performed in a single pediatric academic institution. The OFC was generally offered to those patients considered to be at a lower risk of sesame allergy, therefore creating a selection bias. While no cut-off age, sIgE value, or SPT wheal size precluded challenge, typically the patients who were offered an OFC did not have a history of recent objective allergic symptoms upon ingestion of sesame, and the likelihood of a positive reaction was thought to be less than 50% based on the

provider's clinical experience. Overall, 75% of the patients who underwent sesame-OFC had a sesame-sIgE level <5.0 kU_A/L. Some families declined the OFC because of the concerns for anaphylaxis and/or lack of perceived benefits.⁴⁵ Thus, the relatively high rate of negative sesame OFCs could be explained by the selection bias. All patients underwent open OFCs rather than double-blind, placebo-controlled food challenges (DBPCFCs), thereby increasing the risk of bias being introduced by patient or clinician expectations regarding the likely outcome. The OFC were assessed as positive if patients presented any objective or subjective symptoms. However, after excluding 7 patients with subjective OFC symptoms from the analyses, no differences were observed. In addition, open challenges have been previously validated in pediatric populations, and are more commonly utilized than DBPCFCs in clinical practice⁴⁶. We exclusively used commercial aqueous sesame extract for skin prick testing. Skin prick testing with sesame seeds, oil, or tahini has been reported in previous cases to increase the sensitivity of skin prick tests, as these sources still contain sesame lipophilic antigens, unlike commercial extract, as discussed above²⁷. However, using a standardized commercial extract enabled us to have a homogenous comparable testing method for all the patients. Finally, we had only a small number of patients for whom a Ses i 1-sIgE result was available, potentially leading insufficient power to detect a significant difference between the three tests.

CONCLUSIONS

Sesame OFCs can be performed safely in children and should be especially offered to those children with peanut and tree nut allergy who have evidence of sesame sensitization without prior reactions. Commercially available sesame SPT extract and sesame-sIgE have limited diagnostic accuracy. In our study, sesame SPTs with a commercial extract had a better diagnostic accuracy than sesame-sIgE. We suggest that a sesame-SPT wheal ≤ 6 mm threshold could be utilized as a clinical decision point for offering sesame-OFC in practice. Skin testing with fresh form of

sesame (e.g., sesame paste) could be considered before OFC, especially if skin testing with commercial extract is negative. Our results also suggest that Ses i 1-sIgE has a better diagnostic capacity compared to whole sesame-IgE and should be evaluated further in large cohorts of patients. Better characterization and standardization of the commercial sesame extracts for skin testing and *in vitro* testing reagents is needed to improve diagnostic accuracy.

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533

Legends of figures

Fig 1. Receiver operating characteristic curves for sesame SPT wheal size and sIgE levels along with their AUC.

AUC: Area Under the Curve

Fig 2. Estimated probability curves for failing sesame OFC at given SPT wheal size (A) and sesame sIgE level (B).

Probability curves derived from logistic regression (red lines); dashed lines indicated 95% prediction limits. Crosses represent the failed OFC and open circles, the negatives OFC (multiple crosses and circles are overlapping).

Fig 3. Receiver operating characteristic curves for sesame Ses i 1 levels, sIgE levels and SPT wheal size among the subset of patients with available Ses i 1-sIgE along with their AUCs.

AUC: Area Under the Curve

Table I. Clinical and immunological characteristics of the subjects according to the OFC outcome

	Overall (n=341)	Positive OFC (n= 106)	Negative OFC (n= 235)	<i>P</i> -values	<i>Adjusted OR</i> (95%CI)	<i>P</i> -values
Age at avoidance onset (y), mean $\pm$ SD	1.2 $\pm$ 2.5	2 $\pm$ 2.6	1.1 $\pm$ 2.4	0.15 [†]	1.05 (0.92-1.18)	0.47
Age at first OFC (y), mean $\pm$ SD	7.7 $\pm$ 4.3	7.2 $\pm$ 4.0	7.9 $\pm$ 4.4	0.20 [†]	0.94 (0.87-1.01)	0.11
Duration of sesame avoidance (y), mean $\pm$ SD	6.4 $\pm$ 4.1	5.8 $\pm$ 3.9	6.7 $\pm$ 4.2	0.06 [†]	*	*
Sex (male)	234 (69%)	71 (67%)	163 (69%)	0.66 [‡]		
Atopic comorbidity	309 (91%)	97 (92%)	212 (90%)	0.70 [‡]		
Atopic dermatitis	243 (71%)	82 (77%)	161 (69%)	0.11 [‡]	1.16 (0.62-2.20)	0.81
Asthma	157 (46%)	42 (40%)	115 (49%)	0.11 [‡]	0.93 (0.52-1.68)	0.64
Allergic rhinitis	204 (60%)	59 (55%)	145 (62%)	0.32 [‡]		
Other food allergy	332 (97%)	102 (96%)	230 (98%)	0.38 [‡]		
Prior reaction to sesame	84 (25%)	42 (40%)	42 (18%)	< .001 [‡]	2.60 (1.35-5.09)	<.01
History of anaphylactic reaction to sesame	12 (4%)	9 (8%)	3 (1%)	< .01 [§]	*	*
SPT (mm), median (interquartile range)	4 (1-6)	6 (4-7)	3 (0-5)	< .001 [†]	1.47 (1.33-1.66)	<.01
sIgE (kU _A /L), median (interquartile range)	2.07 (0.93-4.80)	1.88 (0.94-4.67)	2.15 (0.92-4.96)	0.92 [†]		

P-value for comparison between positive and negative OFC; [†]: Two Sample t-test; [‡]: Pearson's Chi-Square test; [§]: Fisher's Exact-test;

* In case of correlated variables, we included the most clinically relevant variable in the model.

Table II. Diagnostic capacity of sesame SPT at various cutoff points (n=339)

Sesame SPT wheal size (mm)	Patients (n)	Patients failing challenge (n)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
≥ 3	239	94	88.7	37.8	39.3	88.0
≥ 4	187	85	80.2	56.2	45.5	86.2
≥ 5	127	68	64.2	74.7	53.5	82.1
≥ 6	87	57	53.8	87.1	65.9	80.6
≥ 7	48	34	32.1	94.0	70.8	75.3
≥ 8	28	23	21.7	97.9	82.1	73.3
≥ 9	17	14	13.2	98.7	82.4	71.4
≥ 10	12	10	9.4	99.1	83.3	70.6
≥ 11	8	7	6.6	99.6	85.5	70.1
≥ 12	5	5	4.7	100	100	69.8

Table III. Diagnostic capacity of sesame-sIgE at various cutoff points (n=332)

Sesame-sIgE (kU _A /L)	Patients (n)	Patients failing challenge (n)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
≥ 0.35	292	92	86.8	11.5	31.5	65.0
≥ 1	238	77	72.6	28.7	32.4	69.1
≥ 2	172	51	48.1	46.5	29.7	65.6
≥ 3	123	42	39.6	64.2	34.1	69.4
≥ 3.29	112	40	37.7	68.1	35.7	70.0
≥ 5	82	25	23.6	74.8	30.5	67.6
≥ 7	52	18	17.0	85.0	34.6	68.6
≥ 10	28	11	10.4	92.5	39.3	68.8
≥ 23.5	6	4	3.8	99.1	66.7	68.7
≥ 50	3	2	0.9	99.6	66.7	68.4
≥ 99	1	1	0.9	100	100	68.3

Table IV. Performance characteristics of Ses i 1-sIgE, sesame-sIgE and sesame-SPT among the subset of patients with available Ses i 1-sIgE

	Overall (n=30)	Positive OFC (n=12)	Negative OFC (n=18)	AUC (IC 95%)
Ses i 1 ‖ (ISU)	0.15 (0.15-1.79)	1.34 (0.15-4.33)	0.15 (0.15-0.15)	0.715 (0.541-0.890)
Sesame sIgE ‖ (kU _A /L)	3.88 (2.09-9.60)	4.41 (2.27-7.79)	3.40 (2.09-9.60)	0.505 (0.275-0.734)
Sesame SPT ‖ (mm)	4.00 (1.25-5.75)	4.75 (3.00-6.00)	4.00 (0.25-5.00)	0.641 (0.430-0.853)

‖ Median (interquartile range)

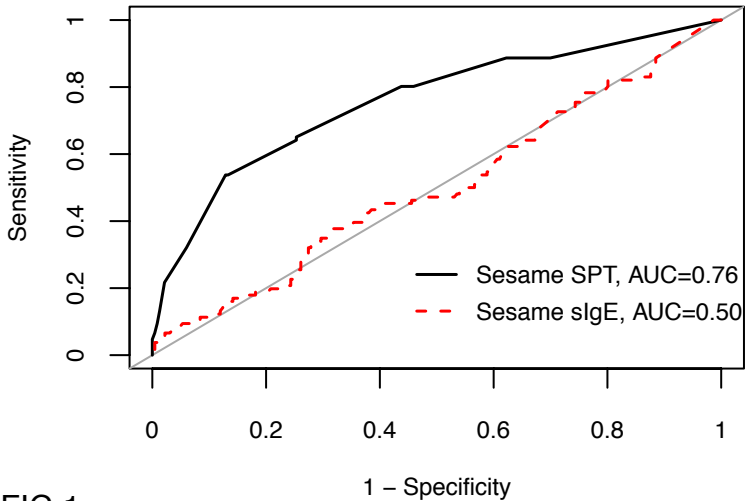


FIG 1

Predicted probability of food allergy

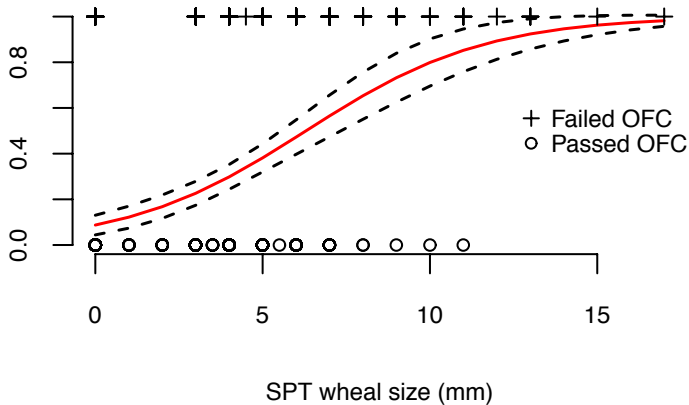


FIG 2-A

Predicted probability of food allergy

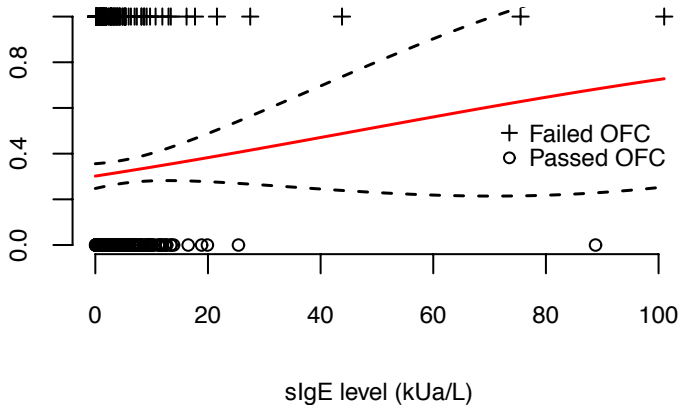


FIG 2-B

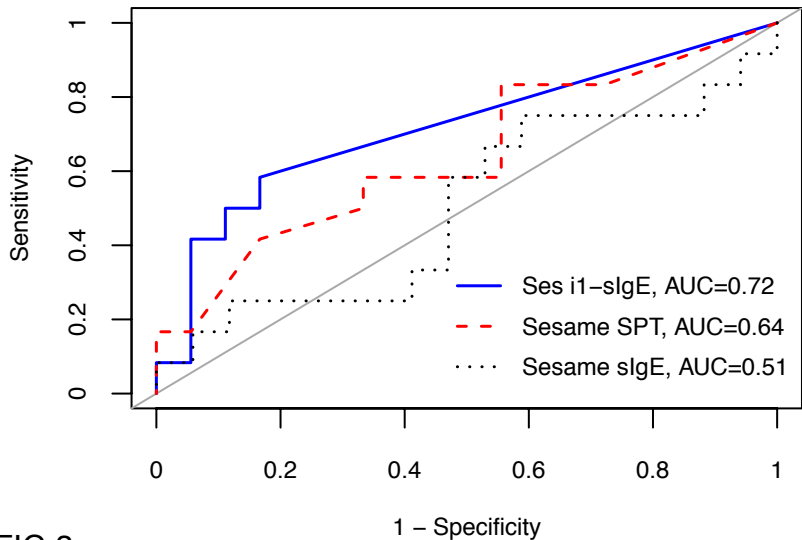


FIG 3

Table E1. Allergic co-sensitizations of the subjects according to sesame-OFC outcome

	Overall (n=341)	Positive sesame-OFC (n= 106)	Negative sesame-OFC (n= 235)
Peanut allergy	136 (40%)	44 (42%)	92 (39%)
Tree nut allergy	124 (36%)	38 (36%)	86 (37%)
Cashew	42 (12%)	14 (13%)	28 (12%)
Pistachio	14 (4%)	2 (2%)	12 (5%)
Walnut	39 (11%)	14 (13%)	25 (11%)
Pecan	13 (4%)	3 (3%)	10 (4%)
Almond	23 (7%)	5 (5%)	18 (8%)
Macadamia nut	5 (1%)	0	5 (2%)
Brazil nut	1 (0.3%)	0	1 (0.4%)
Pine nut	7 (2%)	1 (1%)	6 (3%)
Peanut and / or tree nut allergy	213 (62%)	66 (62%)	147 (63%)
Seed allergy	35 (10%)	10 (9%)	25 (11%)
Mustard	18 (5%)	6 (6%)	12 (5%)
Sunflower	9 (3%)	4 (4%)	5 (2%)
Flaxseed	9 (3%)	0	9 (4%)
Chia	2 (1%)	0	2 (1%)
Poppy	0	0	0

1 **Table E2.** Clinical characteristics of patients with an anaphylactic reaction during the sesame
 2 OFC

Patient	Sex	Prior clinical reaction	Age at OFC (y)	Sesame sIgE (kU _A /L)	Sesame SPT wheal diameter (mm)	Symptoms during OFC	Cumulative eliciting dose of sesame protein (mg)	Medications given during OFC
Patients with a history of reaction to sesame								
#1	male	Er	7.0	2.84	5	Er, TP, N, TS	240	Ce, E, P
#2	male	CW, D, Er, S	7.1	7.37	7	CW, Em, U	191	Ce, Dp, E
#3	male	Em	8.1	43.80	6	AP, CW, R	1803	Ce, Dp, E
#4	male	Em, S	8.4	4.24	7	Em, R, TP	250	Ce, Dp, E
#5	female	Em, UR	3.0	1.10	13	CW, Em, Er	250	Dp
#6	female	Em, Er	10.4	1.30	5	C, CW, R, TP, U	500	Ce, E, Ra
#7	female	C	12.7	3.88	0	Em, S, TP, TS	125	Ce, Dp, E
#8	female	Er	16.8	0.88	9	C, DBP, Em, R, S, TP, U	1125	Dp, E x2
Patients avoiding sesame due to positive testing								
#9	male	-	1.7	<0.35	4	C, Em, S, U	250	Dp, E
#10	male	*	2.2	3.63	5	CW, R, U	250	Ce, Dp, E
#11	male	-	3.1	4.76	4	Em, S, U	515	Dp, E, P
#12	male	-	3.1	8.61	0	AP, U	6000	Ce, Dp, E
#13	male	-	3.3	6.32	4	AP, CW, U	1500	Ce, E
#14	male	-	3.8	1.11	8	CW, TP, U	1803	Dp, E
#15	male	-	4.3	1.12	0	CW, Em, U	750	Dp, E
#16	male	-	4.4	27.5	6	AP, CW, N, TP, U	DM	A, Ce, Dp, P

#17	male	-	5.1	3.33	7	AP, CW, U	250	Ce, E, P
#18	male	-	6.6	75.5	7	AP, U	3	Ce, E
#19	male	-	7.4	5.29	7	AP, CW, R, U	1773	A, Ce, Dp, E, Ra
#20	male	-	10.4	1.13	6	Em, TP, TS, U	500	Ce, Dp, E
#21	male	-	14.9	16.2	6	CW, Em, U	2000	Ce, Dp, E x2, P
#22	male	-	15.6	3.12	17	AP, CW, TP, U	DM	Ce, Dp, E
#23	female	*	17.0	17.7	6	AP, Em, TP, U	500	Dp, E, Ra

3 A, albuterol; AP, abdominal pain; C, conjunctivitis; Ce, cetirizine; CW, cough and wheezing; D,
 4 diarrhea; DBP, decreased blood pressure; DM, data missing; Dp, diphenhydramine; E,
 5 epinephrine; Em, emesis; Er, Erythema; N, nausea; P, prednisolone; R, rhinitis; Ra, ranitidine;
 6 S, swelling; TP, throat pruritus; TS, throat swelling sensation; U, urticaria; UR, unresponsive
 7 * No reaction during an accidental exposure.

Table E3. Clinical characteristics of patients with positive sesame OFC and negative SPT wheal size (0mm)

Patient	Gender	Prior clinical reaction	Age at OFC (y)	Duration of sesame avoidance (y)	Sesame sIgE level (kU _A /L)	Reaction during OFC	Cumulative eliciting dose of sesame protein (mg)	Medications given during OFC
Patients with a history of reaction to sesame								
#1	female	S	3.1	2.3	<0.35	DM	DM	DM
#2	female	TP, U	7.4	0.7	3.36	U	1500	Ce
#3	female	C	12.7	9.2	3.88	Em, S, TP, TS	125	Ce, Dp, E
#4	female	TP	13.3	1.2	6.93	AP, TP, TS	32	Ce
Patients avoiding sesame due to positive testing								
#5	male	-	2.4	2.4	1.95	R, S, U	250	Ce, Dp
#6	male	-	3.1	3.1	8.61	AP, U	6000	Ce, E
#7	male	-	3.2	3.2	0.21	R, U	1500	Ce
#8	male	-	4.3	4.3	1.12	CW, Em, U	750	Dp, E
#9	male	-	6.1	3.1	1.70	AP, Em, Er	125	Ce
#10	male	-	8.1	8.1	1.72	U	773	Ce
#11	female	-	2.0	2.0	5.43	U	DM	Dp
#12	female	-	7.9	7.9	10.70	U	963	Dp

AP, abdominal pain; Ce, cetirizine; CW, cough and wheezing; DM, data missing; Dp, diphenhydramine; E, epinephrine; Em, emesis; Er, Erythema; R, rhinitis; S, swelling; TP, throat pruritus; TS, throat swelling sensation; U, urticaria.

Table E4. Clinical characteristics of patients with positive sesame OFC and negative sesame sIgE level

Patient	Gender	Prior clinical reaction	Age at OFC (y)	Duration of sesame avoidance (y)	Sesame SPT wheal size (mm)	Reaction during OFC	Cumulative eliciting dose of sesame protein (mg)	Medications given during OFC
Patients with a history of reaction to sesame								
#1	male	Er	1.6	0.5	5	U	750	Dp
#2	male	S	2.8	1.9	6	U	DM	Dp
#3	male	Em, L, S, U	3.4	2.5	7	TP, U	500	Ce
#4	male	U	3.6	2.7	7	U	125	Dp
#5	male	C, TP	8.2	8.2	8	R, S, TP	129	Ce
#6	male	U	14.8	12.8	5	TP, U	1015	Dp
#7	female	U	1.4	0.8	5	U	65	Dp
#8	female	S	3.1	2.3	0	DM	DM	DM
#9	female	U	3.5	3.5	4	TP, U	500	Ce
#10	female	U	4.8	2.8	6	U	DM	Dp
#11	female	U	6.1	DM	8	U	258	Dp
Patients avoiding sesame due to positive testing								
#12	male	-	1.7	1.7	4	C, Em, S, U	241	Dp, E
#13	male	-	3.2	3.2	2	R, U	1445	Ce
#14	male	-	3.4	3.4	7	U	1926	Ce

C, conjunctivitis; Ce, cetirizine; DM, data missing; Dp, diphenhydramine; E, epinephrine; Em, emesis; Er, Erythema; L, lethargy; R, rhinitis; S, swelling; TP, throat pruritus; U, urticaria.

Table E5. Clinical characteristics of the subset of patients with available Ses i 1-sIgE according to the OFC outcome

	Overall (n=30)	Positive OFC (n=12)	Negative OFC (n=18)	P-value
Age at avoidance onset (y), mean $\pm$ SD	1.1 $\pm$ 2.1	1.5 $\pm$ 2.5	0.9 $\pm$ 1.7	0.43 [†]
Age at first OFC (y), mean $\pm$ SD	9.5 $\pm$ 3.9	10 $\pm$ 4.8	9.2 $\pm$ 3.4	0.60 [†]
Duration of sesame avoidance (y), mean $\pm$ SD	8.5 $\pm$ 4.2	8.5 $\pm$ 5.5	8.5 $\pm$ 3.0	0.99 [†]
Sex (male)	21 (70%)	7 (58%)	14 (78%)	0.42 [‡]
Atopic comorbidity	29 (97%)	12 (100%)	17 (94%)	1 [‡]
Atopic dermatitis	23 (77%)	10 (83%)	13 (72%)	0.67 [‡]
Asthma	22 (73%)	8 (67%)	14 (78%)	0.68 [‡]
Allergic rhinitis	26 (87%)	11 (92%)	15 (83%)	0.63 [‡]
Other food allergy	29 (97%)	11 (92%)	18 (100%)	0.40 [§]
Prior reaction to sesame	8 (27%)	5 (42%)	3 (17%)	0.21 [§]
History of anaphylactic reaction to sesame	1 (3%)	1 (8%)	0	0.40 [§]

18 P value for comparison between positive and negative OFC ; [†]: t-test; [‡]: Chi²- test; [§]: Fisher-test

Table E6. Diagnostic capacity of Ses i 1-sIgE at various cutoff points

Ses i 1-sIgE (USI)	Patients (n)	Patients failing challenge (n)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
≥ 0.3	10	7	58.3	83.3	70.0	75.0
≥ 1	9	6	50	83.3	66.7	71.4
≥ 3	6	5	41.7	94.4	83.3	70.8
≥ 5	3	2	16.7	94.4	66.7	63.0
≥ 6	2	1	8.3	94.4	50.0	60.7
≥ 30	1	1	8.3	100	100	62.1

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