

Sesame allergy in children: New insights into diagnosis and management

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Abstract

Sesame is a potentially potent allergen that can trigger skin, gastrointestinal, and respiratory tract symptoms, and anaphylaxis. Only 20% to 30% of sesame-allergic children develop tolerance. The prevalence of sesame allergy depends on local diets and ranges from 0.1% to 0.9%. A high risk of accidental exposure to sesame has resulted in mandatory food labeling in many countries. More than half of patients with sesame allergy are also allergic to peanut/tree nuts. Serum-specific IgE testing with a quantitative Ses i 1 component can be performed safely and has higher clinical specificity and better positive predictive value for oral food challenge (OFC) than whole sesame extract or skin prick testing (SPT). Compared with SPT or OFC, in vitro Ses i 1 testing requires no special techniques and carries no risk of reactions. Diagnosis of suspected sesame allergy begins with a thorough history and physical examination. A positive sesame extract test ($\geq 0.1 \text{ kU}_A/\text{L}$) should prompt further testing. In patients with a high probability of reacting, results of component testing may facilitate a decision about performing an OFC. In a Japanese study of OFC and Ses i 1, there was a 5% probability of a positive OFC with Ses i 1 sIgE levels $< 0.13 \text{ kU}_A/\text{L}$, and a 50% probability of a positive OFC with levels $> 32.0 \text{ kU}_A/\text{L}$. Most patients could safely consume sesame if sIgE levels were $< 0.13 \text{ kU}_A/\text{L}$. Ses i 1 testing can be used to guide appropriate management (avoidance, emergency medication, and oral immunotherapy).

KEYWORDS

component-resolved diagnostics, cosensitization, oral food challenge, peanut allergy, Ses i 1, sesame allergy, skin prick testing

1 | INTRODUCTION

Sesame (*Sesamum indicum*) is an important annual oilseed crop from the Pedaliaceae family.¹ The sesame seed hull varies in color, white and black hulls being the most cultivated ones. Seed could be consumed with or without the hull or husk. Unhulled seeds are pale and almost translucent, regardless of the hull color. Sesame is cultivated particularly in Asia and Africa where it is one of the main seed crops.

Its consumption has increased worldwide due to its nutritional values and the spread of African and Asian cuisines globally.

The prevalence of sesame allergy varies widely from 0.1% to 0.9%, affected primarily by the extent to which sesame is incorporated into the local diet. A high risk of accidental sesame exposure in foods, pharmaceuticals, and cosmetics, combined with its demonstrated allergenicity, has resulted in mandatory food labeling in many places such as the European Union, Australia, New Zealand, Canada,

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Morocco, and Taiwan.^{2,3} As of 1 January 2023, sesame joined milk, eggs, fish, shellfish, tree nuts, peanuts, wheat, and soybeans as the ninth food allergen requiring mandatory labeling in the United States.³ The FAO-WHO Joint Expert Group on Food Allergens has recommended that sesame should be included as a priority allergen.⁴

Sesame is a potentially potent allergen that can trigger allergic symptoms in the skin (urticaria), gastrointestinal system (abdominal pain, diarrhea, and vomiting), and respiratory tract (rhinitis, coughing, and wheeze) that can lead to anaphylaxis.^{5,6} Sesame allergy often emerges in childhood and is usually lifelong, with only 20%–30% of children developing tolerance.⁵ Fifty to sixty percent of patients with sesame allergy are also allergic to peanut and/or tree nuts, and sesame has been implicated in the most severe reactions.^{7,8}

Molecular allergology and component-resolved diagnostics (CRD) offer a new tool for allergy specialists as they evaluate suspected cases of sesame allergy. CRD efficiently identifies primary sensitizations, as well as cosensitizations and cross-sensitizations. Serum-specific IgE (sIgE) testing using a quantitative Ses i 1 allergen component has been shown to have higher clinical specificity and better predictive value for positive outcomes of oral food challenge (OFC) than whole sesame sIgE extract or skin prick testing (SPT).^{9–16}

As a marker for primary sesame allergy and severity, Ses i 1 is the most clinically relevant allergen component when assessing the risk of severe allergic reactions.¹⁷ Component testing can identify individuals who are at high risk of reactions to sesame so that they can be appropriately managed with avoidance, and emergency medication, and possibly oral immunotherapy (OIT). CRD has enabled successful immunotherapy for other food allergens based on identification of the primary allergens. OIT for sesame allergy is still in the developmental stage but reportedly has a high rate of success.¹⁶

In this state-of-the-art review, we aim to give keys for a practical approach to sesame allergy diagnosis.

2 | THE PREVALENCE AND NATURAL HISTORY OF SESAME ALLERGY

2.1 | Prevalence of sesame allergy and sensitization

Sesame allergy prevalence varies widely according to geographic location and sesame consumption (Figure 1). In countries with high sesame consumption, such as Australia,^{18,19} Israel^{16,20,21} and Asia,²² sesame allergy confirmed by OFC reportedly occurs in children at rates exceeding 0.4%. A lower prevalence ranging from 0.1% to 0.2% is estimated for Canada,²³ Europe,² Mexico²⁴ and the United States,²⁵ based on patients' self-reported symptoms or physician diagnosis.

Sensitization may occur without any allergic manifestations, and thus the prevalence of sensitization is predictably higher than for confirmed food allergy in the same population. For example, the EuroPrevall study reported prevalence of sesame seed sensitization ranging from 2.86% in Reykjavik to 12.10% in Zurich, in contrast to

Key message

A new quantitative recombinant Ses i 1 test serves as an indicator of primary sesame allergy and could facilitate the diagnosis of sesame allergy, help assess the risk for severe reactions, and support decision-making about the necessity or timing of OFC.

a 0% prevalence of sesame allergy in every center except Reykjavik (0.15%).²⁶ In a large Australian study where sensitization was determined by SPT, the prevalence of sesame sensitization was 1.6% and OFC-confirmed sesame allergy was 0.8%.¹⁹ Of 119 consecutive subjects enrolled in the National Institutes of Health Natural History of Food Allergy protocol, 108 (91%) were sensitized to sesame, 15 (12.6%) had confirmed sesame allergy, and 73 (61.3%) were sesame tolerant.⁶

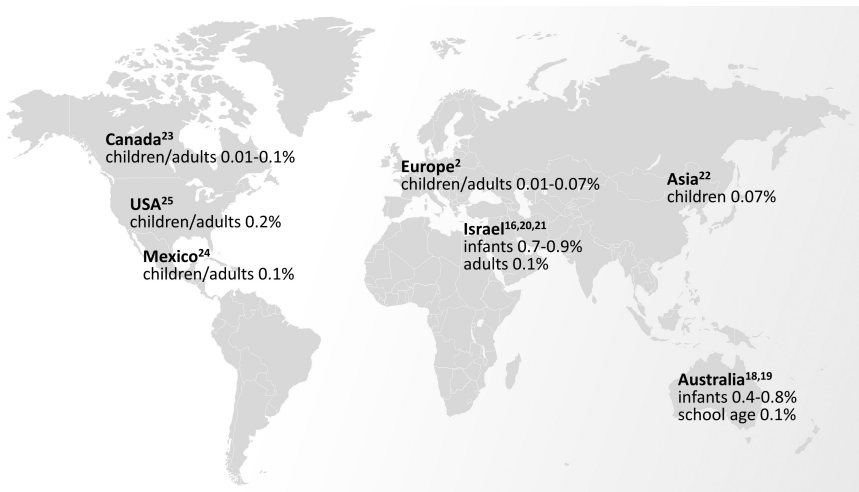
2.2 | The natural history of sesame allergy

The natural history of sesame allergy has been clarified by several recently published studies.

Sesame allergy was confirmed by SPT or OFC in 190 Israeli children, who were followed for almost 4 years. The first appearance of suspected sesame allergy usually occurred in childhood, at a mean age of 11.04 ± 10.2 months.²⁷ Males (66.8%) were more affected than females, and most of the reactions were mild, involving only one organ (skin, conjunctiva, or upper respiratory tract). Forty-one percent had concomitant food allergies, mostly to eggs (14.2%), peanut (12.6%), or tree nuts (10%), and 46.3% had other allergic diseases such as atopic dermatitis, asthma, or allergic rhinitis. Thirty-two percent of these patients had spontaneous resolution of their symptoms confirmed by follow-up OFC or report of dietary sesame consumption. Resolution was significantly more likely to occur in patients who were younger than 10 months old at the time of their first reaction, originally had milder reactions, had a first SPT wheal diameter of <7 mm to commercial sesame extract, and were not allergic to tree nuts. Persistent sesame allergy was significantly associated with being male and older at the time of first allergic reaction, having a more severe initial reaction, and having concomitant food allergies, specifically to tree nuts.

In the United States, suspected sesame allergy was investigated using an online survey, in which 360 clinical reactions were reported in 327 individuals.²⁸ As in the previous study, the reactions were most likely to occur in children ages 1–5 years old (41%) or <1 year old (9.2%), with males more often affected than females (45.6% vs. 36.1%). Two-thirds of the respondents had other food allergies, most commonly to tree nuts (51.7%), peanut (40.1%), egg (25.1%), and milk/dairy (14.1%). Respondents with physician-diagnosed sesame allergy were significantly more likely to have a history of asthma ($p < .001$) and additional food allergies ($p < .001$). Sesame was ingested in most cases (99.4%) and reactions occurred most often at home (63.9%) or at a restaurant (11.7%). Symptoms began within less than 30 min

FIGURE 1 Global prevalence of sesame allergy. Regional differences in sesame allergy prevalence have been attributed to eating habits, environmental exposure, and the age when nuts/seeds are typically introduced.



of consumption in 72.2% of cases, and involved the skin (90.8%), gastrointestinal system (52.5%), respiratory system (51.7%), cardiovascular system (14.7%), or neurologic system (11.4%). Seventy percent of the reactions met criteria for anaphylaxis, and 48% of the reactions required hospitalization.

2.3 | Coexistent peanut and tree nuts allergy

The Pronuts study investigated the challenge-proven rate of coexistent peanut, tree nuts, and sesame seed allergy.⁷ Using the same prospective protocol, allergy centers in London, Geneva, and Valencia recruited children aged 0–16 years who had at least one positive OFC or a history of systemic IgE-mediated reaction to at least one index nut or sesame seed. After SPT or sIgE extract test confirmation of at least one nut or sesame allergy, sequential OFCs were administered for all other nuts and sesame seed. Median age of participants was 4.5 years in London ($n=50$), 6 years in Geneva ($n=42$), and 7.3 years in Valencia ($n=30$). Regional differences emerged in allergy frequency patterns, attributed to eating habits, environmental exposure, and the age when nuts are typically introduced. Overall, peanut allergy was most common (49%) followed closely by walnut (42.6%). Two known co-occurring tree nuts allergies were identified: walnut/pecan allergy, which was more prevalent in Valencia, and cashew/pistachio allergy in Geneva. In London, 48% of participants had multiple nut/seed allergies, compared to 66.7% in Geneva and 73.3% in Valencia. Age >36 months was the most significant predictor of multiple nut/seed allergies, with geographic location also an important predictor based on nut allergies. The severity of allergic reactions during testing did not differ significantly between geographic sites. Almond (33.3%, $n=2/6$), macadamia (31.3%, 5/16), and walnut (30.6%, 11/36) most often required epinephrine treatment during testing, but Brazil nut, sesame, and macadamia produced the highest symptom severity scores, along with more involvement of the lower respiratory tract and cardiovascular system. This study revealed a higher rate of coexistent sesame/nut allergy than previously reported—60.7% of the patients had such coexistent allergies.⁷ More

than half (55.7%) of participants were eating sesame seed before study entry. Interestingly, this rate reached 93% in Valencia, where no cases of sesame allergy were found, which suggests that the timing of nut/seed introduction plays a role in subsequent development of tolerance or allergy. This study group is currently investigating the introduction of nuts to which participants were not allergic, to determine whether that increases the risk of reactions to established nut/seed allergies.

More recently, Bilaver et al. evaluated cross-allergies among an US cohort of 4719 patients by using a national online repository where self and parent-proxy respondents reported at least one physician-diagnosed food allergy. Among the pediatric population ($n=2679$), sesame was reported as a food allergen for 502 children (18.7%), behind peanut (80.1%), tree nuts (70%), egg (53%), and milk (38.9%). Multiple food allergies were reported in 82.5% of this pediatric population. Lower rates of allergy to sesame than previously reported were found among patients with pre-existing allergies to both peanut and tree nuts (25%), tree nuts only (23%), or peanut only (20%). However, the rate of allergies toward peanut or tree nuts in patients with a pre-existing allergy to sesame has not been studied.

Sesame allergy among adults has not been studied extensively. A recent survey of 40,443 US adults (mean age, 46.6 ± 20.2 years) has shown that 25.7% of sesame-allergic responders had an adult onset of their allergy.²⁹ The prevalence of severe reaction was 39%. Multiple food allergies were more common in this adult population with a rate of 80%.

Regarding the other atopic comorbidities, Warren et al. reported in their survey that individuals with sesame allergy were more likely to have several atopic diseases in comparison with individuals without sesame allergy: asthma (27.2% vs. 12.2%), medication allergy (18.8% vs. 11%), eczema (13.7% vs. 6.5%), latex allergies (8.6% vs. 2.0%), insect sting allergies (7.0% vs. 3.5%), food protein-induced enterocolitis (4.4% vs. 0.3%), and eosinophilic esophagitis (3.6% vs. 0.2%).²⁵ Individuals with sesame allergy were also significantly more likely to report a parental history of asthma or eczema compared with those allergic to other top food allergens. Conversely, parents' atopic diseases did not correlate with sesame allergy in infants in the

HealthNuts study.¹⁹ Other than having tree nuts allergies, no other atopic diseases were correlated with the persistence of sesame allergy in Mahlab-Guri's study.²⁷

3 | SESAME ALLERGENS, CROSS-REACTIVITY, AND COSENSITIZATIONS

Sesame has a high content of fat and unsaturated fatty acids from its oily part, which is its main constituent (50%). It also contains proteins (20%), minerals and trace elements (calcium, potassium, phosphorus, iron, etc.), and vitamins. Both proteins and lipid oleosins can trigger allergic reactions.²⁸ The World Health Organization (WHO)/International Union of Immunological Societies (IUIS) lists seven sesame allergen components,³⁰ as described in Table 1. The storage proteins Ses i 1 and Ses i 2 are stable to heat and digestive enzymes, which increase the risk of severe reactions and anaphylaxis.^{17,30,31} Ses i 1 withstands heat as high as 100°C and the acidic and neutral conditions of the gastrointestinal tract. Ses i 1 is regarded as a good predictor of clinical sesame allergy and can elicit dermatologic, respiratory, gastrointestinal, and cardiovascular reactions, as well as anaphylaxis.^{12,17} Ses i 1 has also been identified as a major sesame allergen (>50% prevalence) and as a clinically relevant marker of severe allergic reactions.¹⁷ Sesame oleosins have been characterized as minor allergens,³² although they have also been identified as the dominant allergen in some patients who reported anaphylaxis to sesame.⁵

As noted in Table 1, some sesame components are related to those found in peanut (a legume) and tree nuts (hazelnut, walnut, black walnut, cashew, macadamia, and pistachio) with reported cross-sensitizations. The degree of homology between 2S albumins ranges from 14% to 40%,^{12,31} and cross-reactivity between two proteins

could often be observed when amino acid sequences exceed 70%.³⁹ However, antibodies may bind to specific epitopes in regions that are less variable than the entire protein, allowing cross-reactivity to a higher extent than might be expected by the overall percentage of sequence identity.^{40–42} Figure 2 depicts the property distances between 2S albumins found in various nuts and seeds. For example, the sesame protein components Ses i 1 and Ses i 2 are more closely related to Ana o 3 (cashew), Cor a 14 (hazelnut), and Jug r 1 (walnut) than to the Ara h 2, Ara h 6, and Ara h 7 in peanut.⁴¹ Measuring sIgE to Ana o 3, Jug r 1 and Ses i 1 and Ses i 2 demonstrates the highest relationship with IgE-mediated allergy to cashews, walnuts, or sesame, respectively. Likewise, IgE cross-reactivity between 7S and 11S globulins from sesame and peanuts is common.¹² Ses i 3 and Ara h 1 show 36% homology; however, common IgE-binding epitopes area of both proteins show 80% homology.⁴³ Another study identified the walnut storage protein Jug r 6 (a vicilin) as the cross-reacting protein between sesame and walnut.⁴⁴ Like sesame, walnut contains an 11S globulin (Jug r 4) and 2S albumin (Jug r 1), both seed storage proteins.⁴⁵ Cross-sensitizations also have been reported between sesame and other seeds, such as rye and poppy seeds, albeit clinical significance remains unclear.^{43,46}

The largest study of OFC-proven sesame allergy to date was a retrospective review that evaluated OFC results in 341 pediatric patients attending an allergy clinic in the United States, and reported a 62% rate of cross-sensitization to peanut and/or tree nuts. The rate of cross-sensitization toward other seeds barely reached 9% (mustard, sunflower, flaxseed, poppy, and chia seeds), with no significant difference compared with sesame-tolerant children.¹⁴

Among plant-sensitized subjects in the EuroPrevall study, 63.2% had primary plant source sensitization, and of those 40.9% were based on PR-10 cross-reactivity and 28.5% on profilin or cross-reactive carbohydrate determinants (CCD) cross-reactivity.²⁶

TABLE 1 Allergenic proteins in sesame.

Component	Biochemical name	Molecular weight	Allergenicity	Related proteins
Ses i 1	2S albumin	9 kDa	Represent 15%–25% of total sesame proteins ³³	Related to peanut allergens
Ses i 2	2S albumin	7 kDa	All sesame-allergic patients were sensitized to 2S albumins and had positive IgE binding in two studies. ^{12,34} Ses i 1 and Ses i 2 sensitization was found in 91.7% and 66.7%, respectively, of symptomatic Japanese patients with sesame allergy. ¹² Ses i 1 was more allergenic than Ses i 2	Ara h 2, 6, and 7 ³⁵ Ana o 3 (cashew) Cor a 14 (hazelnut) Jug r 1 (walnut)
Ses i 3	7S vicilin-like globulin	45 kDa	Represent 1%–2% of total sesame proteins ³³ Nearly all patients included in two studies were sensitized to Ses i 3, regardless of their allergic status. ^{12,36}	Ara h 1 (peanut) ³⁵ Ana o 1 (cashew) Cor a 11 (hazelnut) Jug r 2, 6 (walnut)
Ses i 4	Oleosin	17 kDa	Represent 1%–2% of total sesame proteins, but 80%–90% of total oil body proteins ³⁶	Ara h 10 – Ara h 15 (peanut) ³⁵
Ses i 5	Oleosin	15 kDa	Sensitization was demonstrated in 29 of 32 sesame-allergic patients who had systemic reactions ³⁷	
Ses i 6	11S globulin	52 kDa	Represent 60%–70% of total sesame proteins ³³	Ara h 3 (peanut) ³⁵
Ses i 7	11S globulin	57 kDa	Subunits of these proteins were major allergens in a cohort of Italian patients aged 3–73 years ³⁸ 67% of sesame-allergic patients had IgE binding ¹²	Ana o 2 (cashew) Cor a 9 (hazelnut) Jug r 4 (walnut)

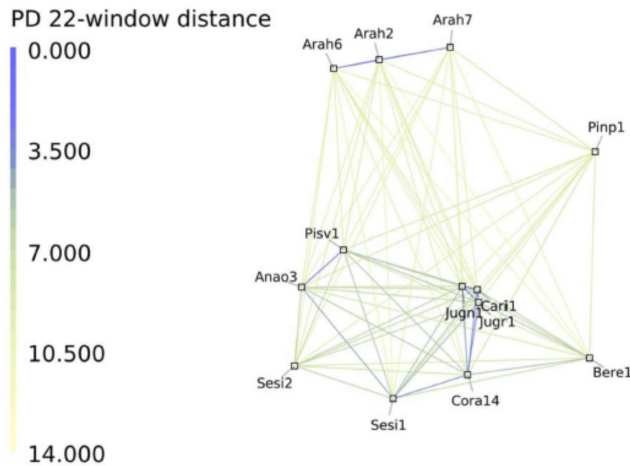


FIGURE 2 Property distances (PD) between unaligned sequences of component proteins.⁴¹ Lower PD indicates higher sequence similarity (i.e., higher similarity in physicochemical properties). For example, walnut/pecan (Jug r 1, Jug n 1, Cari 1) and pistachio/cashew (Pis v 1, Ana o 3) share extensive common sequences. The three peanut allergens (Ara h 2, Ara h 6, and Ara h 7) are most similar to each other, with greater distance from all of the tree nuts and sesame seeds. This figure was published in Dreskin et al.⁴¹ Copyright Elsevier 2021. Used with permission.

4 | DIAGNOSIS OF SESAME ALLERGY

The diagnostic plan for any suspected food allergy begins with a thorough history and physical examination.⁹ The clinical history is crucial and should be reviewed in context of knowledge about the clinical manifestations, patients' age, other atopic diseases (notably other food allergies), and epidemiology of sesame allergy.⁴⁷ The history may identify the sesame source or reveal other potential allergens to which the patient was exposed. Although sesame is a main ingredient in tahini paste and halva sweets, it may also be a hidden ingredient in processed foods such as dips, spreads, bakery goods, and cereals. The diagnostic challenge consists of correctly distinguishing clinically relevant allergic patients from sensitized but sesame-tolerant patients. A clear clinical history alone may be highly convincing of an IgE-mediated sesame allergy, and the tests detailed below would be confirmatory in that case. The usual recommended approach is to assess an IgE-mediated sensitization with a stepwise approach using SPT and/or sIgE. One important thing to remember when analyzing wheal diameter for SPT or sIgE level presented as potential thresholds is that these measurements vary widely according to the studied populations' age and geographic region, among other factors.

4.1 | Skin prick testing

The diagnostic accuracy of SPT using commercial extract has shown inconsistent results, mainly explained by the defatting fabrication process that leads to the removal of allergenic lipid derivatives. SPT performed with sesame paste as tahini, which is easily affordable,

could increase SPT diagnostic performance.¹¹ As tahini could be not broadly available, an easy homemade sesame paste could be an alternative, made from ground, preferably raw, whole white sesame seeds, for example, as this is the most common form consumed.

Epov et al. analyzed retrospectively the diagnostic accuracy of SPT performed with both commercial extract and tahini in 123 children who had a prior reaction to sesame and who underwent a sesame OFC.⁴⁸ Tahini paste increased the sensitivity of the SPT from 33% with the commercial extract to 87%, and reduced the specificity of the test from 86% to 53%. The combination of both tests is suggested by the authors, as it yields a sensitivity of 68% and a specificity of 86%. When considering the variety of native sesame seed used, there was no difference between black, white, and brown sesame seeds in a French study.³⁶

Precautions must be taken while using SPT with native food, as some systemic reactions can occur, notably among young children with a history of anaphylaxis. For example, we have the experience of a 3-year-old girl with a previous anaphylactic reaction (throat oedema, dyspnea, and urticaria) following the consumption of a beef-burger with sesame seeds on top. She had another reaction following the later consumption of beef alone and had a clear beef sensitization (SPT of 12 mm; beef sIgE of 0.22 kU_A/L (ImmunoCAP; Thermo Fisher Scientific)). SPT with tahini to rule out sesame allergy triggered a clear positive SPT with a wheal diameter of 25 mm followed by a systemic reaction with generalized urticaria and rhinoconjunctivitis. Specific IgE tests were positive for both whole sesame and Ses i 1 (5.90 and 2.30 kU_A/L, respectively). Total IgE level was 166 kU_A/L (ImmunoCAP; Thermo Fisher Scientific). She also had a peanut allergy (SPT of 12 mm; peanut and Ara h 2 sIgE of 8.22 and 6.30 kU_A/L, respectively; positive basophil activation test (BAT) to peanut). She passed a beef OFC 2 years later (author experience, used with parental consent).

4.2 | In vitro sIgE testing

Regarding in vitro testing, among sesame-allergic patients, 55%–100% are sensitized to Ses i 1.^{12,17} Positive results for Ses i 1 (≥ 0.1 kU_A/L) suggest that the patient may be at risk for a severe reaction.^{12–16} A previous severe reaction is a risk factor for future severe reactions, but overall the ability to predict reaction severity is limited. In patients with high levels of sIgE to Ses i 1 and a high probability of reacting to sesame, results of component testing may facilitate a decision about when to perform an OFC.^{12–14}

The INTEGRA group has developed recommendations for using two IgE ratios to refine allergy diagnosis: (1) whole extract sIgE to total sIgE or (2) component sIgE to whole extract sIgE.⁴⁹ The first ratio has been used to predict results of OFCs to peanuts or tree nuts.⁵⁰ The second ratio is useful when evaluating food allergens that are under-represented in whole extracts and has been applied to component testing for wheat and hazelnut allergy diagnosis. Additional research may validate similar utility for using these ratios in sesame diagnosis.

4.3 | Basophil activation test

The BAT is a functional assay of growing interest, which could give an overall idea of the patient's phenotype.⁵¹ The BAT, with a high specificity compared with SPT or sIgE alone, has been assessed for several foods. In the Pronuts study, BAT discriminated 8/12 (67%) of sesame-allergic patients from tolerant patients.⁵² Although BAT can be useful in patients in whom previous diagnostic steps do not give a conclusive allergic status before referring for OFC, its implementation is limited. The BAT is time-consuming, requires fresh blood processing soon after collection as well as flow cytometry, and is expensive. Currently, the test is used in research and awaits implementation in daily clinical practice.

4.4 | Oral food challenge

OFC remains the gold standard for the diagnosis of food allergy. However, there is currently no internationally accepted, standardized protocol for OFCs.⁵³ Multiple protocols have been used for sesame OFCs and several protocols predominate in recent sesame studies: the European Academy of Allergy and Clinical Immunology (EAACI) guidelines,⁵⁴ and the PRACTALL protocol⁵⁵ used in the Pronuts study,⁷ which is similar to the National Institute of Allergy and Infectious Diseases (NIAID) recommendations.⁵³ The *EAACI Food Allergy and Anaphylaxis Guidelines* recommend that double-blind, placebo-controlled food challenge (DBPCFC) be performed "when symptoms are subjective, with delayed or atypical symptoms, where patients and/or care givers are anxious, and considered in all research settings."⁵⁵ The guidelines mandate OFC performance in a specialist setting with emergency support immediately available should a severe reaction occur. A 2021 update specifically addresses the management of anaphylaxis following OFC.⁵⁶

The PRACTALL protocol recommends avoiding the challenge food for at least 2 weeks before OFC, testing on an empty stomach, holding medications that may interfere with challenge, having trained medical personnel readily available to treat adverse reactions, and observing patients for at least 2 h after an asymptomatic challenge.⁵⁵ It also recommends administering active and placebo doses on separate days, or separated by a 3-h interval if administered on the same day. A general dosing schedule of 3, 10, 30, 300, 1000, and 3000 mg of food protein, using a form and source of the food that preserves maximum allergenicity, should be administered at intervals of at least 20 min. The guidelines also recommend that a negative DBPCFC end with an open challenge consisting of an age-appropriate portion to confirm tolerance. The evidence level for all of these recommendations is category IV (study of diagnostic yield [no reference standard]).⁵⁵ These guidelines were designed for use in research studies of food allergy and not specifically for sesame OFCs. For practical reasons, testing in nonresearch settings may be open or single-blinded, may not include a placebo control, and may use different forms and doses of sesame administered at different intervals.

The age-appropriate dose would be approximately 18 g of sesame seeds or six teaspoons of tahini paste for patients >3 years old.¹⁴ It should be noted that in the largest retrospective review to date, the median cumulative eliciting dose of sesame protein was 500 mg (equivalent to 2.9 g of sesame seed or ½ teaspoon of tahini).¹⁴ More recently, Turner et al. analyzed sesame dose increase in 246 positive OFCs.⁵⁷ The cumulative eliciting dose predicted to provoke reactions in 5% of the sesame-allergic population (ED05) was 2.5 mg sesame protein. For comparison, the amount of sesame protein described as being consumable by allergic patients without reacting in Ovidia's study was 36 mg sesame protein (10, 20, 40, and 50 whole sesame seeds administered at 20-min intervals), equivalent to an ED25 level of exposure according to Turner's analysis, implying tolerance in ~25% of sesame-allergic individuals.⁵⁸ The authors concluded, "We hypothesize that, when compared with concentrated sesame forms (such as tahini), the diminished allergenicity of intact sesame seeds, as well as the relatively low protein concentration of whole seeds, led to a high rate of passing OFCs." Reaching 1 g of protein (~4 g of tahini paste, approximately one teaspoon) would with good confidence rule out sesame allergy. In addition to sesame seed quantity, Ocak et al. showed that the sesame form used for the OFC is crucial so as not to falsely rule out sesame allergy.⁵⁹ In his recent study, 26/44 children who passed an OFC with sesame seed (approximate total cumulative dose: 1.2–1.9 g, according to age, of sesame protein) failed an OFC with tahini, with some even experiencing anaphylaxis. Shah et al. confirmed that at equal concentration of sesame protein, tahini or sesame paste would probably elicit more reaction and, furthermore, more severe ones, compared with sesame seeds or oil.⁶⁰

In practice, a sesame OFC may start with a small amount of sesame seed, proceed in gradually increasing quantities every 15–20 min, and continue with tahini or a homemade sesame paste, as explained above, to expose the patient to all allergens and concentrations that they might consume, for a cumulative dose of approximately of 1–1.5 g of sesame proteins, according to age.

4.5 | Stepwise approach to sesame diagnosis

Figure 3 summarizes a stepwise approach to diagnosing sesame allergy based on accumulated clinical knowledge at each step and the potential risk associated with different types of allergy testing. At present, a suggestive clinical history of allergy is followed by SPT or sesame whole extract sIgE testing. Because SPT with whole extract has shown inconsistent results for sesame,¹¹ some allergy specialists prefer to add Ses i 1 and Sesame sIgE to their initial diagnostic tests as they provide valuable information, especially regarding the advisability of conducting an OFC. Regarding history of anaphylaxis or high probability of sesame allergy, positive IgE testing solely could confirm sesame allergy and lead to sesame avoidance. SPT in this particular case could lead to an unnecessary discomfort and possibly to a systemic reaction.

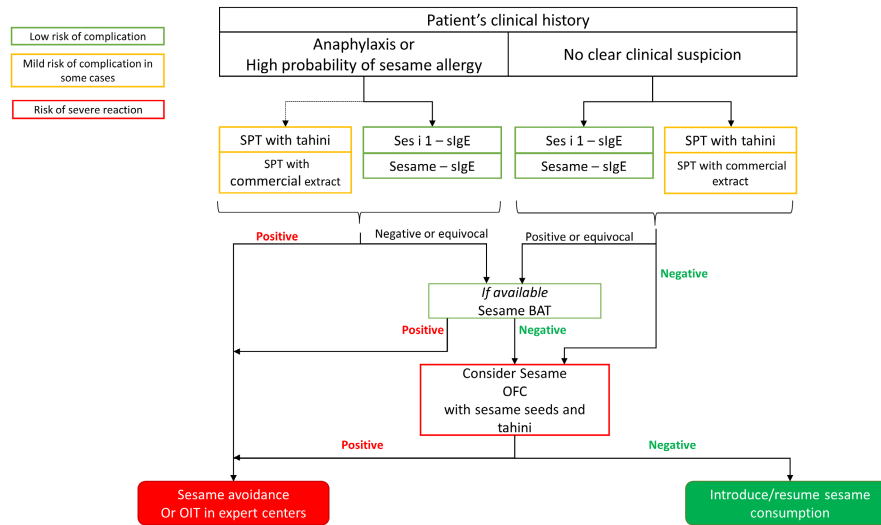


FIGURE 3 Diagnostic pathway for suspected sesame allergy. Our recommended sesame diagnostic pathway is based on accumulated clinical knowledge at each step and the potential risk associated with different types of allergy testing. A suggestive clinical history of allergy is followed by skin prick testing (SPT) or sesame whole extract sIgE testing. Because SPT with whole extract has shown inconsistent results for sesame,¹¹ some allergy specialists prefer to add Ses i 1 and Sesame sIgE to their initial diagnostic tests as they provide valuable information, especially regarding the advisability of conducting an oral food challenge (OFC). Regarding history of anaphylaxis or high probability of sesame allergy, positive IgE testing solely could confirm sesame allergy and lead to sesame avoidance. Skin prick test in this particular case could lead to an unnecessary discomfort and possibly to a systemic reaction. A sesame OFC may start with a small amount of sesame seed, proceed in gradually increasing quantities every 15–20 min, and continue with tahini or a homemade sesame paste (ground, raw, whole white sesame seeds), for a cumulative dose of approximately of 1–1.5 g of sesame proteins, according to age. Once the diagnosis of sesame allergy is confirmed, strict sesame avoidance is recommended. However, OIT could be offered in expert centers. BAT, basophil activation test; OFC, oral food challenge; OIT, oral immunotherapy; SPT, skin prick testing.

A one- or two-step diagnostic pathway that has been studied with cashew allergy could perhaps be used with sesame diagnosis as well.^{61,62} The pathway skips directly from clinical history to component testing alone or to sesame sIgE plus component testing. In cashew allergy diagnosis, both the one- and two-step pathways reduced OFCs by 79%–80% compared with SPT. Using the component Ana o 3 alone resulted in a cost reduction of 46.43% over SPT alone, and using sIgE plus Ana o 3 resulted in a cost reduction of 44.94%.⁶⁸ A similar plan using Ses i 1 alone or with Sesame IgE deserves study.

With regard to sensitivity, it is fair to ask whether false-negative results for SPT or Sesame sIgE will completely rule out sesame allergy. In fact, in our study of 341 patients, negative results with SPT using sesame extract and Sesame sIgE do not necessarily rule out allergy (Figure 4).¹⁴ Three patients in the SPT-negative group and one in the Sesame sIgE-negative group required epinephrine during OFC. Thirty of the 341 patients had negative results for Ses i 1 testing (ImmunoCAP ISAC microarray, Thermo Fisher Scientific, Uppsala, Sweden). During OFC, none of the patients in the negative Sesame or Ses i 1 sIgE groups required emergency treatment, while one in the SPT-negative group did. This result suggests that although negative Ses i 1 sIgE may not rule out sesame allergy, it may at least rule out a severe reaction during OFC.

Once the diagnosis of sesame allergy is confirmed, strict sesame avoidance is recommended. However, OIT could be offered in expert centers.

5 | EXAMINING THE EVIDENCE SUPPORTING DIAGNOSTIC TESTING

5.1 | Update in sesame CRD

In a systematic review, Adatia et al. searched PubMed and EMBASE for original scientific studies pertaining to the diagnosis and management of sesame allergy that were published between 1 November 2006 and 1 November 2016.⁵ Their search identified 268 articles, with 162 abstracts assessed for relevancy and 30 articles ultimately selected. Four CRD studies published between 2010 and 2016 were considered. Three of the four were designed to identify allergenic components in sesame-allergic patients.^{34,38,63} The fourth, conducted by Maruyama et al., used an experimental recombinant Ses i 1 test with the goal of identifying sesame-allergic patients and reliably reducing the need for OFCs.¹² At the time, there was no commercially available component test for Ses i 1, and Adatia et al. concluded that DBPCFC remained the diagnostic gold standard. Since then, several studies have shed light on the utility of Ses i 1 component testing.

5.2 | Ses i 1 component vs. sesame whole extract testing

Maruyama et al. compared the Ses i 1 test that was under development to a commercially available whole extract Sesame IgE.¹²

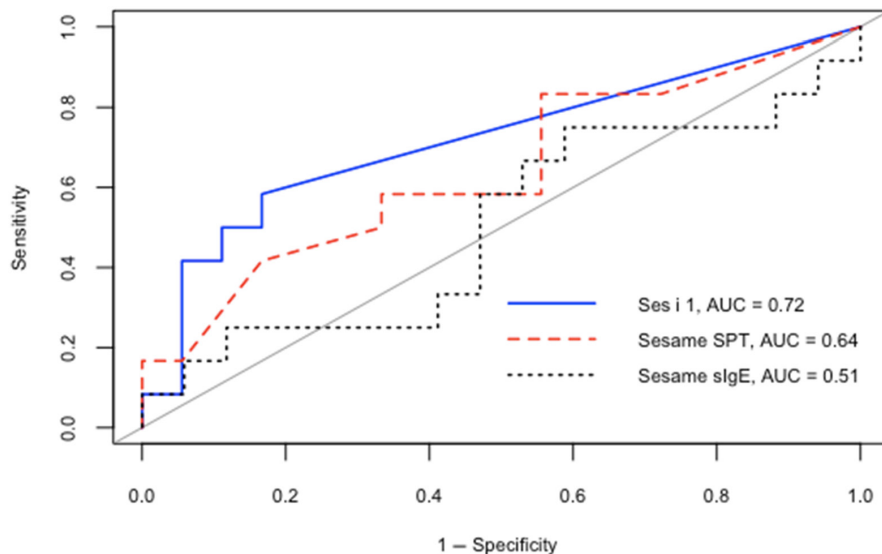


FIGURE 4 Estimated probability for failing oral food challenge with skin prick testing, sesame IgE, or Ses i 1 sIgE.¹⁴ Ses i 1 sIgE from ImmunoCAP ISAC microarray (Thermo Fisher Scientific) had better diagnostic accuracy than SPT or Sesame sIgE, with an area under the curve of 0.72 compared to 0.64 and 0.51, respectively. This figure was published in Saf et al.¹⁴ Copyright Elsevier 2020. Used with permission.

Ninety-two sesame-sensitized children were enrolled and divided into symptomatic (positive sesame OFC or persuasive clinical history, $n=36$) and asymptomatic groups (negative sesame OFC or known sesame tolerance, $n=56$). Ses i 1 sensitization was present in 92% (33/36) of the symptomatic group and in 32% (18/56) of the asymptomatic group. A Ses i 1 sIgE level of $3.96 \text{ kU}_A/\text{L}$ was the optimal cutoff point in this study population, yielding a sensitivity of 86.1% and a specificity of 85.7%. The study also found that Ses i 1 was more diagnostically informative than Ses i 2, the other described 2S albumin in sesame.

5.3 | Ses i 1 component vs. OFC testing

In a 2019 study of OFC and Ses i 1, Yanagida et al. found that OFC-positive patients ($n=18$) had higher levels of sIgE to Ses i 1 than OFC-negative patients ($n=72$), 12.8 and $0.1 \text{ kU}_A/\text{L}$, respectively.¹³ The study found 5% probability of a positive OFC with Ses i 1 sIgE levels $<0.13 \text{ kU}_A/\text{L}$, and 50% probability of a positive OFC with levels $>32.0 \text{ kU}_A/\text{L}$. There was no significant difference in SPT wheal diameter between OFC-positive and OFC-negative patients (12 and 10 mm, respectively). In this study, most sesame-sensitized patients could safely consume it if their sIgE levels were $<0.13 \text{ kU}_A/\text{L}$. The Ses i 1 testing was superior to either SPT or whole sesame extract sIgE for predicting OFC outcome.

In 2021, Goldberg et al. examined the utility of sIgE testing as an alternative to OFC in 42 patients with suspected sesame food allergy.¹⁵ They found significantly different ($p=.001$) levels of sIgE to Ses i 1 between allergic ($n=27$) and tolerant ($n=15$) patients, and these results correlated significantly with the BAT results. Results from both tests yielded correct positive classifications for 25 of 27 sesame-allergic patients, and the authors concluded that results of these two tests could decrease the need for time-consuming, costly, and potentially risky OFC in sesame-allergic patients.

Among 341 sesame-allergic patients, 30 had Ses i 1 sIgE levels measured (ImmunoCAP ISAC microarray).¹⁴ Thirty percent of the patients with sIgE levels to Ses i 1 $>0.1 \text{ kU}_A/\text{L}$ had a negative OFC compared to 69% tested with sesame extract and 61% with a positive SPT (Figure 4). The level of Ses i 1 sIgE was significantly associated with a positive OFC ($p<.05$), whereas the level of sIgE to sesame extract ($p=.98$) or SPT ($p=.20$) did not show an association with a positive OFC. No severe reaction was observed among patients who had negative Ses i 1 sIgE levels and who reacted during the OFC. Conversely, one of the seven patients with negative SPT in the analyzed subgroup experienced anaphylaxis during the OFC. Three other patients had an anaphylactic reaction in the same study with either negative SPT or Sesame sIgE.

6 | THE CLINICAL IMPACT OF CRD FOR SESAME-ALLERGIC PATIENTS

An accurate diagnosis of food allergies has major implications. A false-positive diagnosis could lead to unnecessary restrictions, anxiety, and prescription of emergency medications, while a false-negative test could result in life-threatening reactions.⁴⁷ With its ability to identify and quantify single allergenic components in serum samples, CRD has greatly improved the diagnostic accuracy for IgE-mediated sensitizations and allergies to other foods. In the case of suspected sesame allergy, both whole extract sIgE testing and SPT have not performed as well as Ses i 1 component testing in identifying the presence or severity of clinically relevant symptoms.

Quantitative sIgE testing offers a low-risk method of testing that may determine when or whether OFC is necessary. Compared with either SPT or OFC, Ses i 1 testing requires no special techniques or precautions, and carries no risk of systemic reactions. Compared with BAT, Ses i 1 testing is technically available in the clinic and less expensive.

The Pronuts study underscores the importance of understanding regional patterns when diagnosing nut/seed allergies.⁷ Sesame was not among the top three confirmed allergies in any of the locations, yet it was among the allergens producing the highest symptom severity scores during OFCs. Fear of a mild or a severe reaction during OFC resulted in 11 participants dropping out of this study. The availability of in vitro Ses i 1 testing might allay such concerns, while providing additional information to guide avoidance and treatment strategies.

7 | SESAME ORAL IMMUNOTHERAPY

The management of sesame allergy consist on avoidance of sesame and prompt treatment in case of an allergic reaction. However, the possibility for using OIT in sesame-allergic patients has also been explored. An Israeli research group evaluated sesame OIT in 60 children age 4 or older diagnosed with sesame allergy on the basis of OFC.¹⁶ Fifteen patients maintained a sesame elimination diet and served as controls. A subset of 16 patients who received OIT had their immunologic parameters measured at the start and end of their treatment. Fifty-three patients treated with OIT (88.4%) were fully desensitized to sesame; four additional patients were desensitized to >1000mg sesame protein. Thus, 57 of 60 patients (95%) achieved partial or full tolerance, whereas none of the patients in the control group did. Treated patients had significant decreases in Ses i 1 sIgE ($p = .007$) and basophil reactivity ($p = .001$). More than 6 months after reaching maintenance OIT levels with only mild reactions, 47 patients passed the 4000-mg challenge. The authors concluded that sesame OIT is an effective alternative to sesame avoidance in allergic children.

In another study, quality of life for children aged 8–12 years who underwent OIT improved significantly ($p < .001$) during up dosing and among those who completed a follow-up visit ($p < .001$) compared with controls.⁶⁴ Parents reported better quality of life than their children did at every stage of OIT.

OIT with in-clinic up dosing and home treatment was used for seven sesame-allergic adults in Israel and none failed therapy.⁶⁵ Rates of severe reactions at home and of treatment failure were low and comparable with rates in younger patients.

The use of quantitative Ses i 1 testing coupled with effective OIT holds new promise for patients with sesame allergy. One strategy would be to offer Ses i 1 testing to children with evidence of sesame sensitization but without previous reactions. The results could then guide a decision about OFC, and that outcome could lead to OIT when appropriate.

8 | CONCLUSIONS

Ses i 1 is a relevant component for determining primary sesame allergy and assessing the risk for severe reactions. Component testing with Ses i 1 has higher clinical specificity and better predictive value for positive outcomes of OFC than whole extract Sesame sIgE

or SPT. Patients who are reluctant to undergo OFC can be tested with Ses i 1 without fear of anaphylaxis and the resulting information used to guide appropriate management, whether it be avoidance, provision of emergency medication, or OIT.

AUTHOR CONTRIBUTIONS

Sarah Saf: Conceptualization; writing – review and editing; investigation; methodology; writing – original draft. **Magnus P. Borres:** Conceptualization; methodology; writing – review and editing; writing – original draft. **Eva Södergren:** Conceptualization; writing – review and editing; writing – original draft; methodology.

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