

# Sesame allergy: current perspectives

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**Abstract:** Sesame is an important global allergen affecting ~0.1% of the North American population. It is a major cause of anaphylaxis in the Middle East and is the third most common food allergen in Israel. We conducted a systematic review of original articles published in the last 10 years regarding the diagnosis and management of sesame allergy. Skin prick testing appears to be a useful predictor of sesame allergy in infants, although data are less consistent in older children and adults. The diagnostic capacity of serum-specific immunoglobulin E is poor, especially in studies that used oral food challenges to confirm the diagnosis. Double-blind, placebo-controlled food challenge thus remains the diagnostic gold standard for sesame allergy. The cornerstone of sesame allergy management is allergen avoidance, though accidental exposures are common and patients must be prepared to treat the consequent reactions with epinephrine. Novel diagnostic and treatment options such as component-resolved diagnostics, basophil activation testing, and oral immunotherapy are under development but are not ready for mainstream clinical application.

**Keywords:** sesame allergy, skin prick testing, specific IgE, component-resolved diagnostics, epinephrine autoinjector

## Introduction

Sesame (*Sesamum indicum*) is a seed native to the Middle East and Africa, where it has been cultivated as an oilseed crop for >3000 years. It is traditionally consumed as a paste called tahini or as a sweet called halva and is also used as toppings on breads and crackers, particularly in Western countries. The population prevalence estimates of self-reported sesame allergy in the USA<sup>1</sup> and Canada<sup>2,3</sup> range from 0.1% to 0.2%. Studies report prevalence estimates of 0.1% in Canadian children<sup>3</sup> and up to 0.8% among children in Australia.<sup>4</sup> The rate of sesame-induced anaphylaxis varies significantly by region, with much higher rates reported in the Middle East compared to those in North America. Sesame is reported as the second most common food to cause anaphylaxis in Israeli children, accounting for 43% of cases<sup>5</sup> and the third most common food to cause anaphylaxis in Saudi Arabia,<sup>6</sup> but it was responsible for only 2.8% of food-induced anaphylaxis cases in Canadian children.<sup>7</sup> Despite its relatively low prevalence in North America, sesame allergy is important to recognize given that sesame allergy is rarely outgrown and the risk of accidental reactions is high.<sup>8–10</sup>

In this systematic review, we assess the literature published in the last 10 years regarding sesame allergy with a focus on the diagnosis and management of this important global allergen.

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## Methods

We (MB-S and AA) searched the PubMed and EMBASE databases for original scientific studies pertaining to the diagnosis and management of sesame allergy. We used the search criteria “sesame” AND “allergy” and then limited the results to articles published between November 1, 2006, and November 1, 2016, that were written in English and French. The abstracts of the resulting papers were then reviewed and those relevant to the diagnosis and management of sesame allergy were included in the systematic review and have been summarized in Tables 1 and 2. The initial PubMed and EMBASE database queries yielded a total of 268 articles, which was reduced to 162 after applying the above filters and then further narrowed to 30 articles after the 162 abstracts were assessed for relevancy to the systematic review (Figure 1).

## Diagnosis

### Skin prick testing (SPT)

SPT is a key component in the diagnosis of food allergy. In 2013, the HealthNuts study, a population-based, longitudinal food allergy study in Melbourne, Australia, examined the diagnostic performance of sesame SPT in infants aged 11 to 15 months. Sesame SPT data were available in 103 patients who had a conclusive oral food challenge (OFC). The 95% positive predictive value (PPV) threshold was 8 mm or greater (95% confidence interval [CI], 5–9 mm), which corresponded to a sensitivity and specificity of 48% and 99%, respectively. However, the PPV of a wheal 3 mm or greater, a threshold commonly used to define a “positive” SPT, was ~58%.<sup>11</sup> Receiver operator characteristic (ROC) curve analysis showed the test was highly accurate with an area under the curve (AUC) of 0.92. Similarly, in an Israeli cohort of 16 children and adults who underwent OFC because of a clinical history suggestive of sesame allergy, a positive SPT (which was defined as wheal size equal to or greater than the wheal size of the histamine control, though all but one patient had a wheal diameter of 3 mm or greater) had a PPV of 88%, supporting the diagnostic value of sesame SPT.<sup>10</sup>

However, other studies have not strongly supported the diagnostic utility of sesame SPT. Permaul et al found that a positive SPT (wheal more than 3 mm greater than negative control) had 71% sensitivity, 58% specificity, 31% PPV, and 88% negative predictive value (NPV) using OFC as the gold standard in a retrospective study of children aged 2–12 years. ROC curve analysis showed lower accuracy compared to the HealthNuts study with an AUC of 0.67, and a 95% PPV threshold could not be calculated.<sup>12</sup> The same research

group obtained similar results in a second retrospective chart review of patients aged 6.6 months to 19.6 years, in which a positive SPT had 43.5% sensitivity, 64.3% specificity, 14.3% PPV, and 89.3% NPV, though in this study, the diagnostic performance measures were calculated using a convincing reaction history as the gold standard.<sup>13</sup> The apparent inconsistent performance of SPT in the literature is likely related to differences in the populations studied, particularly with respect to age and geographical area. In addition, Permaul et al<sup>12</sup> included primarily peanut allergic patients who had positive sesame allergy screening tests, which may have contributed to the low rate of positive OFCs that they observed. Those positive tests could represent clinically inconsequential cross-reactivity between peanut-specific immunoglobulin E (IgE) and sesame, a possibility that is supported by the significant homology that exists between sesame and peanut allergens.

### Skin-prick-prick (SPP) testing

SPP testing, which is an SPT that uses sesame seeds, oil, or tahini instead of a commercial extract, may also be useful when investigating possible sesame allergy. Sesame seeds are typically crushed and suspended in saline for ease of administration,<sup>14</sup> whereas sesame oil and tahini can be applied to the skin undiluted.<sup>15</sup> The relative quantities of the major sesame allergens in sesame seed, oil, and tahini have not been systematically studied, though the preparation procedures used to make sesame oil and tahini, including roasting, are not thought to reduce their allergenicity.<sup>15,16</sup>

A British group evaluated the diagnostic performance of SPP testing using tahini in a retrospective cohort of 79 children. They found that a 2 mm wheal threshold yielded the best sensitivity (70%) and specificity (73%).<sup>17</sup> Sesame SPP testing has also been proposed as a tool to diagnose sesame allergy in patients with negative SPT and serum-specific IgE (sIgE). Della-Torre et al<sup>15</sup> reported a case of a 55-year-old male with suspected sesame allergy who had negative SPT and sIgE but positive SPP testing using tahini. Similarly, Barbarroja-Escudero et al evaluated 10 patients with convincing histories of sesame allergy and negative SPT and found that 9 had positive SPP tests using sesame seeds. They posited that cases of sesame allergy with negative SPTs may be accounted for by the absence of lipophilic antigens within commercial sesame extracts due to defatting procedures used during the production process. In their cohort, immunoblotting using each patient’s serum demonstrated IgE binding to oleosins, allergenic sesame proteins that are fat soluble.<sup>18</sup>

Table 1 Articles regarding the diagnosis of sesame allergy

Modality	Type of study	Author, pub yr	Ref #	Peds/ adult	Country of study	Findings	Comments
SPT and sIgE	Prospective cohort	Peters et al, 2013	11	P	Australia	In infants aged 11–15 months, the 95% PPV threshold for SPT was 8 mm. A 95% PPV threshold could not be calculated for sIgE; the 86% PPV was 50 kU <sub>a</sub> /L.	OFC was undertaken irrespective of wheal size, so the 95% PPV threshold identified is informed by the full spectrum of possible SPT responses.
SPT and sIgE	Prospective cohort	Cohen et al, 2007	10	P and A	Israel	In a cohort of 44 patients with convincing histories of reactions to sesame, all 44 had positive SPTs, and of the 12 who underwent sIgE testing, 9 had an elevated sIgE. 14/16 patients had a positive OFC. 20% of sesame-allergic patients developed tolerance after a mean follow-up length of 6.7 years.	A positive SPT was defined as wheal size equal to or greater than the wheal size of the histamine control, though all but one patient had a wheal diameter of 3 mm or greater.
SPT and sIgE	Retrospective	Permaul et al, 2009	12	P	USA	A positive sIgE demonstrated 71% sensitivity, 31% specificity, 22% PPV, and 80% NPV. The overall accuracy was poor with an ROC curve AUC of 0.56. Similarly, a positive SPT demonstrated 71% sensitivity, 58% specificity, 31% PPV, and 88% NPV. ROC curve analysis for SPT showed an AUC of 0.67. A 95% PPV decision point could not be calculated for either sIgE or SPT.	Only 21% of the OFCs performed were positive, possibly because subjects in the study were peanut- or tree nut-allergic patients who were screened for sesame sensitization and found to be positive, rather than coming to clinical attention because of a suspected reaction to sesame.
SPT	Retrospective	Sturtius et al, 2010	13	P	USA	A positive SPT was found to have a sensitivity of 43.5%, a specificity of 64.3%, PPV of 14.3%, and NPV of 89.3%. Children with a history of allergic reactions to both peanuts and tree nuts were more likely to have an allergic reaction to sesame (OR = 10.2, 95% CI, 2.7–38.7)	Sesame allergy was determined by physician documentation of convincing history of reaction.
SPP testing and sIgE	Retrospective	Foong et al, 2013	17	P	UK	In a cohort of children up to 18 years of age, the highest sensitivity and specificity of SPP testing using tahini was achieved with a 2 mm wheal cutoff, which provided a sensitivity of 70% and a specificity of 73%. The highest sensitivity and specificity of sIgE was achieved with a cutoff of 1.7 IU/mL, which provided a sensitivity of 77% and a specificity of 85%.	Only 79 of 214 (37%) of patients identified as having possible sesame allergy from the retrospective review returned the questionnaire by which tolerance to sesame was determined. 25 of the 79 underwent OFC to confirm the presence or absence of sesame allergy.
SPP testing	Case report	Della-Torre et al, 2013	15	A	Italy	A 55-year-old male with a history of severe anaphylaxis to sesame bread was found to have negative sesame SPTs, sIgE, component-resolved diagnostics, and SPP testing with crushed sesame seed. However, SPP testing with tahini and BAT was positive.	SPP testing may be of value when sesame allergy is strongly suspected but initial investigations are negative. Tahini may be a useful source of sesame allergens for SPP testing.
SPT and SPP testing	Case series	Barbarroja-Escudero et al, 2015	18	A	Spain	Among 10 patients with negative SPTs to sesame but convincing histories of sesame allergy, 2 had positive sIgE tests and 9 had positive SPP tests. Immunoblotting showed IgE binding to oleosins in all patients.	Sesame-allergic patients may have negative SPTs because sesame extracts used for SPT are produced using defatting procedures and oleosins are lipid soluble.

(Continued)

Table 1 (Continued)

Modality	Type of study	Author, pub yr	Ref #	Peds/ adult	Country of study	Findings	Comments
Immediate-reading contact test	Case report	Alonzi et al, 2011	16	A	Italy	Two patients with suspected sesame allergy were found to have negative SPT, sIgE, and SPP testing but both had positive immediate-reading contact tests (involves applying a square of filter paper soaked in sesame oil to the volar aspect of a patient's arm and assessing for a wheal-and-flare reaction after 20 minutes). Sesame allergy was confirmed in both patients by OFC.	Isolated allergy to sesame oleosins may explain the negative SPT, sIgE, and SPP testing (to crushed sesame seed in saline) but positive immediate-reading contact test. SPP testing using sesame oil was also performed but was negative, possibly because the oil was wiped off the patients' arms immediately after the prick, so there may have been insufficient time for the oils to diffuse into the skin.
sIgE	Retrospective	Zavalkoff et al, 2008	19	P	Canada	In children aged 2–18 years, a sIgE cutoff of 7 kU <sub>a</sub> /L yielded a 71.4% sensitivity, 90.4% specificity, and when calculated using a sesame allergy prevalence of 1%, a 7.9% PPV, and a 99.7% NPV. A 95% PPV threshold could not be determined. No sesame-allergic patient had a negative sIgE test.	Patients were classified as sesame allergic based on a suggestive history and positive SPT, except for 3/28 who underwent OFC. They underwent sIgE measurement several years after the index reaction, raising the possibility that the measured sIgE corresponded to resolved sesame allergy in some cases.
sIgE	Cross-sectional	Maloney et al, 2008	20	P and A	USA	95% PPV threshold for sIgE could not be calculated. No patient with an undetectable sIgE was found to be sesame allergic.	The sensitivity and specificity of different sIgE concentrations were not provided.
sIgE	Retrospective	Tuano et al, 2016	21	P	USA	The median sIgE for the patients who achieved tolerance to sesame decreased from 12.9 kU <sub>a</sub> /L at diagnosis to 2.95 kU <sub>a</sub> /L. Among six peanut-allergic patients with sesame sensitization (but no history of reaction to sesame), sesame sIgE was as high as 5.52 kU <sub>a</sub> /L (median 1.04 kU <sub>a</sub> /L).	These sIgE values are based on just 3 patients, only one of whom had retesting prior to an OFC. The other two reintroduced sesame at home, so the time between confirmation of tolerance and the repeat sIgE measurement is unknown. In the absence of more robust data, the authors suggest a rechallenge threshold of 2 kU <sub>a</sub> /L.
Component-resolved diagnostics	Experimental	Maruyama et al, 2016	22	P	Japan	Sensitization to a recombinant 2S albumin (rSes i 1) had greater AUC from ROC analysis compared to the commercially available ImmunoCAP with a sensitivity and specificity of 86.1% and 85.7%, respectively, at the optimal cutoff point.	Caution should be exercised when interpreting sesame sIgE in peanut-allergic patients as the value may be unexpectedly high, possibly because of cross-reactivity between sesame allergen Ses i 3 and peanut allergen Ara h 1.
Component-resolved diagnostics	Experimental	Teodorowicz et al, 2016	23	A	The Netherlands	Oleosin was the dominant allergen in five patients who had a history of anaphylaxis to sesame.	The presence or absence of sesame allergy was determined using an OFC in 74% of the patients; the remaining patients had a convincing history of reactivity or tolerance, so OFC was not performed.

Component-resolved diagnostics	Experimental	Asero et al, 2014	<sup>24</sup>	P and A	Italy	Six previously unrecognized sesame allergens were found to elicit IgE reactivity in the sera of up to 10 sesame-allergic patients. One sesame allergen showed IgE reactivity in 10/10 patients' sera. All 18 sesame-allergic patients tested were sensitized to the basic subunits of 11S globulin.	Further investigation into these allergens for component-resolved diagnostics may significantly improve the sensitivity of laboratory testing for sesame allergy. Patient blood samples were analyzed using a 2-dimensional electrophoretic method combined with immunoblotting.
Component-resolved diagnostics OFC	Experimental	Magni et al, 2010	<sup>25</sup>	P and A	Italy	The lowest dose of sesame protein predicted to elicit a reaction in 5% of the sesame-allergic population (lower bound of the 95% confidence interval of the ED <sub>05</sub> using discrete dosing) was 0.13 mg of sesame protein.	Dano et al <sup>27</sup> included the data from the 21 patients used in the analysis of Taylor et al and added DBPCFC data from an additional 14 patients. Both studies used the Weibull probability distribution model to calculate the most conservative ED <sub>05</sub> thresholds.
OFC	Retrospective	Taylor et al, 2014	<sup>26</sup>	P and A	Various	The most sensitive sesame-allergic patients had a no observed adverse effect level of 0.85 mg of sesame protein and a discrete lowest observed effect level of 1.02 mg of sesame protein. The lowest dose of sesame protein predicted to elicit a reaction in 5% of the sesame-allergic population was 1.0 mg of sesame protein.	Patients were not excluded on the basis of severity of previous reactions, so bias toward higher tolerated doses is minimized. A semilog OFC dosing scheme that is informed by the range of reaction thresholds observed and can be completed in 1 day is provided.
Inhalational challenge	Case report	Dano et al, 2015	<sup>27</sup>	P and A	France	A 7-year-old female, who developed recurrent episodes of bronchoconstriction when at her parents' bakery, was suspected to have sesame allergy. Her initial testing showed a sesame SPT of 8 mm and a sIgE of >100 IU/L. OFC was thought to be too risky, so the diagnosis was confirmed by spirometry after she handled sesame seeds for 15 minutes, which resulted in a 21% decrease in FEV1.	The patient was not known to have ever tried or handled sesame, so the suspected route of sensitization was inhalation. In cases of suspected sesame-induced bronchospasm, spirometry after handling sesame seeds may be helpful to confirm the diagnosis.
BAT	Case report	Caimmi et al, 2011	<sup>28</sup>	P	Italy	A 47-year-old male with suspected sesame allergy had negative SPT, sIgE, and SPP testing (to sesame paste and seeds), but BAT was clearly positive. Sesame allergy was confirmed with a DBPCFC.	BAT can be useful in the investigation of patients with suspected sesame allergy who have negative initial testing.
BAT, SPT, and sIgE	Experimental	Raap et al, 2011	<sup>40</sup>	A	Germany	BAT had better diagnostic accuracy compared to sIgE with an AUC of 0.904 compared to 0.870 and was correlated with DBPCFC severity scores, in a mixed group of patients with one or more food allergies.	Of the 76 subjects enrolled in the study, only 6 were sensitized to sesame.
BAT	Experimental	Song et al, 2015	<sup>41</sup>	P and A	USA	Recombinant Ses i 6 activated basophils that were passively sensitized with sesame-allergic sera obtained from 19 sesame-allergic patients.	Component-resolved diagnostics using BAT is a promising technique but requires further study to assess diagnostic performance.
BAT	Experimental	Wallowitz et al, 2007	<sup>42</sup>	A	USA	BAT, double-blind, placebo-controlled food challenge; ED05, eliciting dose 5%; FEV1, forced expiratory volume in 1 second; NPV, negative predictive value; OFC, oral food challenge; P, pediatric; Peds, pediatric; PPV, positive predictive value; ROC, receiver operator characteristics; sIgE, serum-specific immunoglobulin E; SPP, skin prick prick; SPT, skin prick testing.	

**Abbreviations:** A, adults; AUC, area under the curve; BAT, basophil activation test; DBPCFC, double-blind, placebo-controlled food challenge; ED05, eliciting dose 5%; FEV1, forced expiratory volume in 1 second; NPV, negative predictive value; OFC, oral food challenge; P, pediatric; Peds, pediatric; PPV, positive predictive value; ROC, receiver operator characteristics; sIgE, serum-specific immunoglobulin E; SPP, skin prick prick; SPT, skin prick testing.

**Table 2** Articles regarding the management of sesame allergy

Modality	Type of study	Author Pub yr	Ref #	Peds/ adult	Country of study	Findings	Comment
Prevention Prenatal	Case-control	Hsu et al, 2013	29	P	USA	Maternal consumption of sesame seed during pregnancy was associated with increased rates of sesame sensitization in the child.	Whether maternal consumption of sesame seed during pregnancy increased the risk of sesame allergy, not just sensitization, was not assessed. 46% of the peanut/tree nut/sesame-sensitized children had never consumed sesame.
Prevention Infancy	RCT	Perkin et al, 2016	32	P	UK	Enquiring about tolerance study: introduction of sesame at 3 months of age did not decrease the incidence of sesame allergy compared to standard introduction at 6 months of age (irrespective of whether perprotocol or intention-to-treat analyses were used) after 3 years of follow-up.	The study was not powered to detect a difference between the early and standard introduction groups specifically for sesame.
Prevention Infancy	RCT	Perkin et al, 2016	33	P	UK	Enquiring about tolerance study: multiple allergenic foods, including sesame, can be introduced into the infant diet safely without adversely impacting breastfeeding.	Only ~44% of patients in the early introduction group adhered to the sesame introduction protocol.
Allergen avoidance	Cross-sectional	Zurzolo et al, 2013	35	N/A	Australia	Of 1355 prepackaged products from a supermarket in Melbourne, Australia, 6.1% listed sesame as an ingredient and 27.5% included a precautionary statement regarding sesame. The most common types of food that included precautionary labeling for sesame were savory biscuits (86%), bread products (73.3%), and sweet biscuits (71.1%).	Precautionary labeling for sesame is common in countries such as Australia where it is a priority allergen, and therefore, patients must be educated to interpret such labeling.
Accidental exposures	Cross-sectional	Segal et al, 2016	8	P	Canada	62% children with sesame allergy presented with anaphylaxis. The annual rate of accidental exposure was 15.9%. At least 14 of the 16 children experiencing an accidental exposure possessed an EAI, but only 1 used it.	This is the largest North American study of children with sesame allergy.
Development of tolerance	Cross-sectional	Gupta et al, 2013	9	P	USA	Of 114 patients with a history of sesame allergy, 27.1% achieved tolerance at a mean age of 5.9 years.	This is the largest North American study assessing the development of tolerance to food allergens including sesame.
Development of tolerance	Cross-sectional	Aaronov et al, 2008	36	P	Israel	Of the 30 children with sesame allergy identified, only 9 achieved tolerance (at an average age of 2.8 years).	All the food allergic children were followed for a mean of 4.7 years (minimum 1 year), though the average duration of follow-up specifically for the sesame-allergic patients was not provided.
Complementary medicine	RCT	Wang et al, 2015	38	P and A	USA	Significantly more subjects treated with placebo compared to FAHF-2 had improvements in consumed allergen dose at the DBPCFC undertaken 6 months after the baseline DBPCFC.	Patients allergic to sesame, peanut, tree nut, fish, and shellfish were included. Peanut was the study allergen for 73.5% of the subjects. Subgroup analysis for the sesame-allergic group was not published.
Oral immunotherapy	Open-label randomized trial	Bégin et al, 2014	43	P and A	USA	Oral immunotherapy to 5 food allergens simultaneously was safe. All the patients who completed the study achieved the target 10-fold increase in reaction threshold.	Adherence was poor with 44% of patients taking <80% of the required tablets for at least one-third of the study. The study included 6 sesame-allergic patients who received sesame immunotherapy. Since the study was a phase I trial, it was not designed for the evaluation of efficacy.

**Abbreviations:** A, adults; DBPCFC, double-blind, placebo-controlled food challenge; EAI, epinephrine autoinjector; FAHF-2, Food Allergy Herbal Formula-2; N/A, not applicable; P, pediatrics; Peds, pediatrics; pub yr, publication year; RCT, randomized controlled trial.



**Figure 1** Results of the systematic literature review using the PubMed and EMBASE databases.

**Note:** Excluded papers did not pertain to the diagnosis or management of sesame allergy or were reviews rather than original articles.

An Italian group has also described an “immediate-reading contact test” for sesame allergy, which involves the application of a square of filter paper soaked in sesame oil to the volar aspect of a patient’s arm and assessing for a wheal-and-flare reaction after 20 minutes. This test was positive in two patients (with OFC-confirmed sesame allergy) who had negative SPT, sIgE, and SPP tests. The authors also attributed their results to the presence of oleosins within sesame oil.<sup>16</sup>

### Serum-specific IgE concentration

Measurement of serum concentrations of IgE specific to a food antigen (sIgE) is also an important diagnostic tool in the investigation of food allergies. However, two studies suggest that sesame sIgE concentration has poor diagnostic performance. The HealthNuts study described earlier found that the highest PPV threshold that could be calculated was 86%, which corresponded to a sIgE of 50 kU<sub>a</sub>/L or greater. The diagnostic accuracy of sIgE was low with an AUC of 0.76 on ROC curve analysis.<sup>11</sup> These results were similar to previously published data from Permaul et al,<sup>12</sup> which showed that a positive sIgE test had 71% sensitivity, 31% specificity, 22% PPV, 80% NPV, and low overall accuracy with an ROC curve AUC of 0.56.

These results are inconsistent with the data from a British group that evaluated the diagnostic performance of sIgE in a retrospective cohort of 79 children. They found that a relatively low threshold of 1.7 IU/mL provided a sensitivity of 77% and specificity 85%, but OFC was only performed in 25 of the patients, so the remaining patients were classified as sesame allergic or nonallergic based on clinical history.<sup>17</sup> Similarly, Zavalkoff et al<sup>19</sup> found that, in children aged 2–18 years, a sIgE cutoff of 7 kU<sub>a</sub>/L yielded a 71.4% sensitivity and 90.4% specificity, but again only 3 of the 28 subjects underwent OFC. A decision point for the 95% PPV could not be determined. Since no sesame-allergic patient had an undetectable sIgE, the authors suggested that sIgE could be useful to exclude rather than diagnose sesame allergy. These findings were corroborated by Maloney et al who also found that all sesame-allergic patients had detectable sIgE concentrations and that the test was not sufficiently predictive to calculate a 95% PPV threshold,

in American children and adults. However, the study was similarly limited by the small number of OFCs performed and by the exclusion of patients with inconclusive clinical histories.<sup>20</sup> The use of an undetectable sesame sIgE to rule out sesame allergy was not supported by Permaul et al<sup>12</sup> who, using OFC as the diagnostic standard, reported that 29% of sesame-allergic patients had sIgE below the detection threshold.

Caution must also be exercised when interpreting sesame sIgE in patients with other preexisting food allergies. Tuano et al showed that sesame sIgE can be as high as 5.52 kU<sub>a</sub>/L in peanut-allergic patients who tolerate sesame. The suspected mechanism behind elevated sesame sIgE in some peanut allergic patients is cross-reactivity between sesame allergen Ses i 3 and peanut allergen Ara h 1.<sup>21</sup> Though not yet studied, similar contaminant increases in sesame sIgE may also be found in patients allergic to other foods whose allergens cross-react with sesame allergens.

### Component-resolved diagnostics

Recently, it has been reported that IgE testing to food allergen components can increase the accuracy of specific IgE testing. This method measures the serum concentration of IgE antibodies to specific allergenic proteins within food and is an area of significant interest to reduce the number of OFCs required. The World Health Organization/International Union of Immunological Societies’ Allergen Nomenclature Subcommittee has registered seven sesame allergy components – two 2S albumins (Ses i 1 and Ses i 2), one vicilin-like 7S globulin (Ses i 3), two oleosins (Ses i 4 and 5), and two 11S globulins (Ses i 6 and Ses i 7). However, to date very few studies have evaluated this technique in sesame allergy. In one study of 92 children sensitized to sesame, sensitization to a recombinant form of the protein 2S albumin (rSes i 1) had a comparable sensitivity to the commercial assay measuring sIgE (86.1% for rSes i 1 compared to 83.3% for the commercial assay) but significantly better specificity (85.7% compared to 48.2%) for sesame allergy.<sup>22</sup> Teodorowicz et al<sup>23</sup> identified the major allergens in six sesame-allergic patients and found that oleosin was the dominant allergen in the five patients who had a history of anaphylaxis to sesame, leading to the hypothesis that sensitization to oleosin may identify a more severe sesame-allergic phenotype.

One of the barriers to the application of component-resolved diagnostics in sesame allergy is that a number of allergenic proteins and protein subunits of sesame have not yet been identified. An Italian group showed that all 10 of the sesame-allergic patients they studied were sensitized to at least one unregistered protein.<sup>24</sup> Magni et al<sup>25</sup> applied a

2-dimensional electrophoretic method combined with immunoblotting and found that all the sesame-allergic patients studied were sensitized to the basic subunits of 11S globulin.

## Food challenge

The gold standard for diagnosing sesame allergy remains the double-blind, placebo-controlled food challenge (DBPCFC), though for practical purposes unblinded OFCs without a placebo control are usually employed. OFC is considered when the history is not convincing or the patient has never been exposed, but the patient tests positive for sesame sensitization by SPT or sIgE. Dano et al used data from 35 DBPCFCs to determine the no observed adverse effect level (NOAEL), defined as the largest amount of food that an individual can ingest without causing an adverse reaction, and the lowest observed adverse effect level (LOAEL), the lowest dose of an allergen ingested that produces an adverse effect. They included data from 21 patients that had already been collated and analyzed by the Voluntary Incidental Trace Allergen Labeling program<sup>26</sup> and collected data from 14 additional patients. The lowest discrete NOAEL recorded was 0.85 mg, and the lowest discrete LOAEL recorded was 1.02 mg of sesame protein. The lowest dose of sesame protein predicted to elicit a reaction in 5% of the sesame-allergic population (i.e., the eliciting dose 5% [ED<sub>05</sub>]) was 1.0 mg. Based on these data, an OFC dosing scheme with the following semilog increments was suggested: 0.3, 3, 30, 100, 300, 1000, and 3000 mg of sesame protein.<sup>27</sup>

In addition to OFC, sesame inhalation challenges may be useful in specific circumstances. Caimmi et al reported a case of a 7-year-old-female who developed recurrent episodes of bronchoconstriction when at her parents' bakery. Her initial testing showed a sesame SPT of 8 mm and a sIgE of >100 IUA/L. OFC was considered too risky, so the diagnosis was confirmed by spirometry, which demonstrated a 21% decrease in her force expiratory volume in 1 second after she handled sesame seeds for 15 minutes.<sup>28</sup>

## Management

### Primary prevention

The development of methods to prevent food allergy is a major area of clinical allergy research. One case-control study assessed the effect of sesame consumption during pregnancy, and one randomized controlled trial (RCT) evaluated the effect of early introduction in the first months of life.

In a case-control study of 1272 children, Hsu et al assessed whether maternal sesame seed protein exposure

during pregnancy, in the form of progesterone formulated in sesame seed oil for luteal support or maternal consumption of sesame seeds, increased the risk of sensitization to peanuts, tree nuts, and/or sesame in the child. They found that progesterone oil formulation exposure was not associated with increased odds of the child being sensitized to peanut, tree nut, and/or sesame. Women who consumed sesame seeds during pregnancy were more likely to have a child that was sensitized to one or more of peanut, tree nut, and sesame (OR 1.78, 95% CI 1.08–2.92 for sesame consumption during the first trimester), but whether the sensitized children had true food allergy was not confirmed.<sup>29</sup> Maternal avoidance of allergenic foods during pregnancy is not currently recommended by allergy guideline societies.<sup>30,31</sup>

In a large RCT, the enquiring about tolerance (EAT) study assessed whether the introduction of sesame (as well as five other allergenic foods) at 3 months of age in exclusively breast-fed infants reduced the likelihood of developing sesame allergy compared to the introduction of sesame after 6 months of age. They concluded that there was no difference in the incidence of sesame allergy in the early and standard introduction groups after 3 years of follow-up.<sup>32</sup> However, since the primary outcome of the EAT study evaluated allergy to one or more of six allergenic foods, not just sesame allergy, it was not sufficiently powered to detect a difference in the incidence of sesame allergy between the two groups. Furthermore, only 44% of patients were compliant with the early introduction regimen for sesame.<sup>33</sup>

### Allergen avoidance

One of the mainstays of food allergy management is allergen avoidance. Successful avoidance requires patients to have accurate information on the ingredients and possible allergenic contaminants in food, and consequently several countries have developed regulations for food allergen labeling. The European Union, Australia, New Zealand, and Canada have listed sesame as one of the allergens for which there are food-labeling requirements. A notable exception is the USA where the current regulatory framework does not recognize sesame as a priority allergen.<sup>34</sup>

To study the prevalence of precautionary allergen labeling, an Australian study evaluated 1355 prepackaged products from one supermarket in Melbourne, Australia. They found that 6.1% of items listed sesame as an ingredient and 27.5% of items included a precautionary statement regarding sesame. Sesame was the third most common allergen listed on such precautionary labels. The most common types of food that included precautionary labeling for sesame were



savory biscuits (86%), bread products (73.3%), and sweet biscuits (71.1%).<sup>35</sup>

When educating patients about the avoidance of such foods, it may be helpful to describe the quantity of sesame seeds that could trigger a reaction in a highly sensitive patient. Since a sesame seed weighs ~3.2 mg (corresponding to ~0.544 mg of sesame protein) and the lowest reported LOAEL is 1.02 mg, just two sesame seeds could trigger an allergic reaction,<sup>27</sup> supporting the need for careful allergen avoidance.

Despite strict food avoidance, accidental exposures can occur. In a Canadian study, the parents of 115 children with a known diagnosis of sesame allergy were surveyed on whether their children had experienced an accidental exposure. Accidental exposures were relatively common with an annual rate of 15.9%. Older children were more likely to experience an accidental exposure, possibly due to increased risk-taking behaviors and less supervision.<sup>8</sup> This is an important finding given that the development of tolerance to sesame appears to be relatively uncommon. In a cross-sectional study that surveyed parents of food allergic children, an American group showed that only 27.1% of sesame-allergic children achieved tolerance.<sup>9</sup> Cohen et al<sup>10</sup> similarly noted that 20% developed tolerance in their cohort after a mean follow-up length of 6.7 years and an Israeli group found that 30% of sesame-allergic children achieved tolerance after a mean follow-up time of 4.7 years.<sup>36</sup>

## Epinephrine autoinjector (EAI)

Given that the first-line treatment in case of an accidental reaction is prompt epinephrine administration, patients with a sesame allergy must keep an EAI available at all times, recognize the signs and symptoms of anaphylaxis, and reliably self-administer the medication when necessary (or have a parent do so if the patient is a young child). However, the Canadian study discussed earlier showed that <10% of sesame-allergic patients who experienced an accidental exposure used their EAI. Equally worrisome was that of the 49 patients who already possessed an EAI prior to their initial reaction to sesame, only 6 used the device.<sup>8</sup>

The prescription of an EAI should not be considered a benign intervention. Pinczower et al found in a cross-sectional study of 103 children, 17 of whom had sesame allergy, that prescription of EAI negatively affected health-related quality of life. When required, the prescription of an EAI should be accompanied by patient education with regular reinforcement.<sup>37</sup>

## Complementary and alternative medicine

Traditional Chinese medicine (TCM) has attracted interest in Western countries as a source of alternative medicine for a variety of diseases, including food allergy. The most extensively studied drug for food allergy that originated from TCM is Food Allergy Herbal Formula-2 (FAHF-2), a nine-herb formula based on the traditional Chinese formula *Wu Mei Wan*. As previous phase 1 trials had demonstrated its safety and murine models had shown encouraging immunomodulatory effects, an RCT was undertaken to assess its efficacy. A total of 58 subjects with food allergy, including sesame, underwent a baseline DBPCFC and a second DBPCFC after 6 weeks of treatment with FAHF-2 to assess for an increase in the dose of allergen eliciting a reaction. FAHF-2 was not found to be efficacious, however, as significantly more subjects treated with placebo compared to FAHF-2 had improvements in consumed allergen dose at the follow-up DBPCFC, though its safety and beneficial in-vitro immunomodulatory effects were again demonstrated. Subgroup analysis for the sesame-allergic group was not published.<sup>38</sup>

## Future directions

### Basophil activation testing (BAT)

BAT is a novel in-vitro diagnostic tool with emerging applications in food allergy diagnosis. Stimulation of basophils with allergen to which they are sensitive induces the expression of cell-surface proteins, and these proteins can be detected with specific antibodies using flow cytometry. CD63 is the most common marker under study, though several other candidate markers have been identified.<sup>39</sup> Studies evaluating the use of BAT in the diagnosis of sesame allergy are highly limited. A German group reported a case of a 47-year-old male with suspected sesame allergy who had a negative SPT, sIgE, and SPP testing to sesame seeds and paste. BAT was strongly positive, however, and sesame allergy was confirmed by DBPCFC, suggesting a role for BAT in the diagnosis of sesame allergy.<sup>40</sup> In a study of a mixed group of patients with one or more food allergies, including sesame, BAT was found to have better diagnostic accuracy compared to sIgE with an AUC of 0.904 compared to 0.870 and was correlated with DBPCFC severity scores. However, only 6 of the 67 patients enrolled were sensitized to sesame, so specific conclusions regarding the use of BAT in the diagnosis of sesame allergy were not possible.<sup>41</sup> Methods for using BAT with sesame protein components are also under development but remain experimental.<sup>42</sup>

## Immunotherapy

Oral and sublingual allergen-specific immunotherapies have been proposed as possible disease-modifying treatments for food allergy. Most such immunotherapy protocols involve the provision of progressively higher doses of the allergen with the goal of modulating the immune response to the allergen. If desensitization is achieved, patients can eat larger quantities of the allergen without triggering a reaction, but they must consume the allergen daily. If true tolerance is achieved, a state of sustained unresponsiveness develops in which the patient can consume usual quantities of the food intermittently with no reactions. Studies have shown some success using these methods with food allergens such as milk, peanut, and egg, but up to this point the efficacy of sesame immunotherapy has never been systematically studied. Bégin et al, however, demonstrated the safety and feasibility of oral immunotherapy using multiple food allergens simultaneously in 25 patients, 6 of whom were sesame-allergic and received sesame immunotherapy. All the patients who completed the study achieved the target 10-fold increase in reaction threshold, though as a phase 1 trial, the study was not designed for the evaluation of efficacy.<sup>43</sup>

## Conclusion

The diagnosis of sesame allergy currently relies on the clinical history supplemented by testing for sesame sensitization and OFC in certain cases. SPT appears to be more informative compared to sIgE in children and adults, though data in adults remain highly limited. Novel diagnostic tools including component-resolved diagnostics and BAT for the diagnosis of sesame allergy are also under development. The mainstays of management include the prescription of an EAI and patient education regarding allergen avoidance and prompt use of epinephrine in case of an accidental reaction. The induction of tolerance by immunotherapy is an attractive management option that is under investigation. Future studies of novel diagnostic methods and management techniques will transform how allergy to sesame, a major allergen of increasing importance, is approached in the years ahead.

## Disclosure

The authors report no conflicts of interest in this work.

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