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Clinical reactivity to soy is best identified by component testing to Gly m 8

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Food allergy; soy; component testing; skin prick testing; IgE; oral food challenge; receiver operating characteristic curve; sensitivity; specificity

To the Editor

Soy allergy affects approximately 0.4% of young children in the US.[1] A majority of children with soy allergy will become tolerant over time,[2] making it important that allergists reassess these patients on a regular basis. An accurate assessment of patients with a suspected soy allergy is vital, since avoidance of soy is extremely difficult, it is a common ingredient in processed foods, and consumption of soy-containing food additives (soy isolate, soy concentrate, and soy flour) is increasing in Western diets. Diagnosis of soy allergy is complicated by a high rate of false positives on routine IgE testing, as several studies have identified a dissociation between high levels of specific IgE (sIgE) to soy proteins and low rates of clinical symptoms.[3,4] While a soybean sIgE level of 30 kU_A/L has been reported to achieve 94% specificity in predicting clinical reactivity, this level carries a sensitivity of only 44%.[4]

This study examines the utility of skin prick tests (SPT), soy sIgE and component testing, for diagnosing allergy to soy. Phadia Immunology Reference Laboratory (PiRL, Portage, MI) developed commercial IgE testing to the soy components Gly m 4, 5, and 6, and recently developed testing to the component Gly m 8, a 2S albumin. Previous studies on soy components have yielded conflicting results. In 2011, Ito et al. reported that Gly m 5 and 6 were associated with severe clinical reactions caused by soybean in Japanese children, and that analysis of IgE antibodies to Gly m 5 and Gly m 6 will most likely better predict soybean allergy than an extract-based test.[5] In 2012, Fukutomi et al. reported that, in their Japanese cohort, a high level of IgE to recombinant Gly m 4 was associated with adult soybean allergy.[6] More recently, Ebisawa et al. reported that IgE to the 2S albumin Gly m 8

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was significantly greater in children reactive to soy than those who were asymptomatic, while IgE levels to Gly m 5 and Gly m 6 were not.[7] Klemans et al. also reported that Gly m 8 had the best accuracy in diagnosing soy allergy, although the AUC for this component was comparable to SPT and sIgE to soy extract.[8] Limitations of these previous studies examining soy components include their geographic limitations to Europe and Asia, their utilization of patients diagnosed with soy allergy without confirmation by OFC, and their comparison of IgE levels from subjects with soy allergy to negative controls who were known to tolerate soy and have significantly lower soy sIgE levels.[5-8] Here we analyze IgE results to the components Gly m 4, 5, and 6, as well as the new 2S albumin component, Gly m 8, among children from the US who underwent OFCs for the evaluation of suspected soy allergy.

The study protocol was approved by the Institutional Review Board (IRB) of the Icahn School of Medicine at Mount Sinai. The soy OFCs were performed at the Jaffe Food Allergy Institute, a Pediatric, university-based outpatient practice, between December 2006 and September 2013. Patients were referred for open OFC by our allergists on the basis of their clinical impression. No cut-off age, sIgE value or SPT wheal size precluded challenge. Typically these patients did not have a history of recent objective allergic symptoms upon ingestion of soy, and most demonstrated sensitization to soy with 35/40 (87.5%) having a positive SPT (1 did not have this test performed), and 40/41 (97.6%) patients having detectable sIgE (>0.35 kU_A/L) to soy extract. Charts were reviewed for demographic data, SPT results (extract from Greer, Lenoir, NC), and OFC outcomes. The OFCs were performed per published guidelines, with most challenges using doubling doses every 15 minutes until an age-appropriate serving size was ingested.[9] For subjective symptoms, challenges were temporarily halted, and then continued following resolution of symptoms if the supervising physician deemed it safe to proceed. Treatment decisions were based on the supervising clinician's judgment.

Soy component testing was performed on sera obtained within 1 year of an OFC to soy from patients participating in an IRB-approved study evaluating component testing to a variety of foods or from subjects who had serum banked as part of the Food Allergy Resource Initiative. IgE to soy extract and the components Gly m 4, 5, 6, and 8 were measured with the ImmunoCAP system. Differences between groups were analyzed with the Mann-Whitney U-test for non-parametric data; a *P*-value of <0.05 was considered significant for all tests. The diagnostic value of each test was assessed with an area under the receiver operating characteristic (ROC) curve (AUC).

Demographic data and test results from 41 patients who underwent a soy OFC (median age 7 years, 73% male) are shown in Table E1 (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). Overall, 18 (44%) of the challenges elicited a reaction. There was no difference between those who tolerated vs reacted to soy in median age or sex, or the presence of coinciding peanut allergy, although there was a significant difference between the 2 groups in median SPT wheal diameters (median wheal 3 mm vs 5 mm, p=0.006). There was a high rate of peanut allergy in both groups, with 38/41 (93%) subjects carrying a diagnosis of peanut allergy (22/23 (96%) of the soy tolerant and 16/18 (89%) of the soy-reactive subjects).

Component testing was performed on the 23 children who passed the soy OFC and the 18 who failed. Of those who failed, symptoms included vomiting (9 subjects), urticaria (7 subjects), throat discomfort or pruritus (6 subjects) and respiratory distress including repetitive coughing or wheezing (4 subjects). Almost all (40/41) patients had a sIgE to soy extract >0.35 kU_A/L, with a median soy sIgE level of 7.78 kU_A/L among the clinically non-reactive subjects, and 16.4 kU_A/L among the clinically reactive patients (p=0.08).

While almost all subjects (40/41) also had a sIgE to Gly m 8 >0.35 kU_A/L, the median sIgE to this component was significantly lower in the clinically non-reactive subjects compared to the reactive subjects (1.43 kU_A/L vs 5.03 kU_A/L, p<0.001). There were no significant differences seen among the median sIgE levels to the other soy components, including Gly m 4, 5, or 6 (Table I). Specific IgE to the soy component Gly m 8 had the highest AUC to discriminate between soy-allergic and soy-tolerant subjects (0.82, see Table E2 and Figure E1 in this article's Online Repository at www.jaci-inpractice.org). The AUCs for soy extract (0.66) and the components Gly m 4 (0.56), Gly m 5 (0.67) and Gly m 6 (0.62), were much less discriminatory. The AUC for the SPT wheal diameters (0.74) was slightly lower than that of Gly m 8.

The sensitivity, specificity, positive and negative predictive values, and the percent misclassified, defined as the total percentage labeled as either allergic or non-allergic in error, were calculated using the optimal cutoff point for the soy extract and each component (Table II). There was a high rate of misclassification observed for the optimal cutoffs for SPT and IgE to soy extract and the various components, with a Gly m 8 cutoff of 3.55 kU_A/L misclassifying 9 of 41 subjects (22%). While this percentage is relatively high, the optimal cutoff for Gly m 8 misclassified 4 (9.7%) fewer subjects than any other sIgE test. Sensitivity and specificity to Gly m 8 were also calculated for different IgE levels (see Table E3 in this article's Online Repository at www.jaci-inpractice.org).

In summary, sIgE testing for soy allergy results in many false positive tests and unnecessary dietary elimination. Among a population of children referred for OFCs to establish the diagnosis of allergy to soy, the accuracy of soy testing is improved when utilizing soy components if it includes Gly m 8, although OFCs are still necessary given the high rate of misclassification. Gly m 8 is equally sensitive to SPT, the soy sIgE and other soy components, but more specific for predicting clinical reactivity.

Limitations of this study include the fact that outpatient OFCs were performed openly. While performing the challenges in an open manner may be expected to lead to a higher incidence of subjective symptoms being reported by subjects, over three quarters of the reactions included objective symptoms (14/18, 78%). As opposed to some past trials examining soy component testing, all subjects underwent an OFC. The primary limitation of this study is the small sample size. OFCs to soy are not performed in our practice as often as OFCs to foods such as milk, egg, peanut or tree nuts, possibly due to the prevalence of each food allergy, although it may also reflect hesitancy by our practitioners to pursue OFCs in patients who frequently have markedly elevated soy sIgE levels.

This study reports the limitations of food specific IgE levels and currently available component testing in making a diagnosis of soy allergy as demonstrated by 41 OFCs to soy, and it is the first to report the benefits of using serum IgE levels to the soy component Gly m 8 in a US pediatric population. It is a common occurrence to encounter patients who demonstrate highly elevated sIgE levels to soy or the components that are currently commercially available, despite being able to tolerate this food in his or her diet. Component testing using the soy 2S albumin, Gly m 8, could give a better indication of patients who are clinically reactive to soy, although it still results in a relatively high rate of misclassification. Additional studies with larger cohorts in different geographic regions will be needed to establish specific diagnostic values to increase its value in clinical practice.

Extended Data

Table E1

Demographic data and test results of patients with soy OFCs

	All Patients (n = 41)	Negative OFC (n = 23)	Positive OFC (n = 18)	P Value
Median Age, years, (IQR)	7.0	7.0 (4.0-8.0)	7.5 (5.75-10.75)	0.82
Sex, male, no. (%)	30 (73%)	19 (83%)	11 (61%)	0.12
SPT wheal size in mm (range)	4.0 (0.0-8.0)	3.0 (0.0-6.0)	5.0 (0.0-8.0)	0.006
Median soy sIgE kU_A/L (range)	12.60 (0.27->100)	7.78 (1.00-60.10)	16.40 (0.27->100)	0.08
Peanut Allergy (%)	38 (93%)	22 (96%)	16 (89%)	0.57
Median peanut sIgE kU_A/L (range)	83.2 (3.03- >100)	42.5 (3.03- >100)	>100 (3.45- >100)	0.12

Table E2

Area under the curve (AUC) of soy extract, component sIgE levels, and SPT

Diagnostic Test	AUC (95% CI)
Soy extract	0.66 (0.49-0.84)
Gly m 4	0.56 (0.37-0.75)
Gly m 5	0.67 (0.50-0.84)
Gly m 6	0.62 (0.44-0.80)
Gly m 8	0.82 (0.70-0.95)
SPT	0.75 (0.60-0.91)

CI, confidence interval

Table E3

Sensitivity and Specificity of IgE levels to Gly m 8

	Sensitivity (%)	Specificity (%)
IgE to Gly m 8 (kU_A/L) ≥		
0.35	100	8.7

	Sensitivity (%)	Specificity (%)
1.65	94.4	56.5
3.55	77.8	78.3
7.00	53.8	91.3

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Implications

SPT, sIgE and previously available component testing for soy allergy produce many false positive results. Gly m 8 may be a better marker of clinical reactivity to soy, but still misclassifies many patients.

Table I

Median IgE levels to soy extract and components

	Clinically Nonreactive (n=23)	**Clinically Reactive (n=18)**	
	Median IgE Level kU_A/L (range)	Median IgE Level kU_A/L (range)	P value
Soy Extract	7.78 (1.00-60.10)	16.4 (0.27->100)	0.08
Gly m 4	0.62 (<0.10-17.30)	0.50 (<0.10->100)	0.54
Gly m 5	5.39 (<0.10-28.50)	13.85 (<0.10-45.00)	0.07
Gly m 6	7.73 (<0.10-65.40)	17.15 (<0.10->100)	0.19
Gly m 8	1.43 (0.27-11.70)	5.03 (1.57-20.70)	<0.001
	Median SPT Wheal Size mm (range)	Median SPT Wheal Size mm (range)	
Soy Extract	3.0 (0.0-6.0)	5.0 (0.0-8.0)	.006

Table II

Diagnostic characteristics of sIgE levels at optimal cutoff points for soy extract and components

	Optimal sIgE Cutoff (kU_A/L)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Percent Misclassified
Soy Extract	30.75	44.4	87.0	72.7	66.7	31.7
Gly m 4	12.00	33.3	91.3	75.0	63.6	34.1
Gly m 5	2.74	88.9	43.5	55.2	83.3	36.6
Gly m 6	12.15	61.1	65.2	57.9	68.2	36.6
Gly m 8	3.55	77.7	78.3	73.7	81.8	22.0
	Optimal SPT Wheal Cutoff (mm)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Percent Misclassified
Soy Extract	>3 mm wheal	82.4	60.9	60.9	82.4	30.0