



Pro/Con Debate

Pro: Skin prick testing with fresh foods

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Skin prick test (SPTs) are an essential tool in the hands of the allergist for the diagnosis and follow-up of patients with food allergy. For SPTs to be optimal, they need to have a high accuracy for diagnosis and be standardized to create 95% cutoffs that are consistent between different batch and company preparations. To determine whether fresh foods should be used for skin testing, we need to ask ourselves whether they perform better than commercial extracts in any of these requirements.

In terms of diagnostic utility, both the accuracy of the test (sensitivity and specificity) and its application at the population level (negative predictive value [NPV] and positive predictive value [PPV]) must be considered. An example highlighting the low sensitivity of testing with extract compared with fresh food is the oral allergy syndrome (OAS). The OAS results from sensitization to labile allergens that are present in fresh fruits and cross-react with certain inhalant allergens. These allergens are typically destroyed during the manufacturing process of commercial extracts, resulting in a very low sensitivity when using them. Although in the overwhelming majority of cases a misdiagnosis for OAS would not put the patient at risk, for most food allergies it is essential that SPTs be highly sensitive and that their NPVs be very high to avoid false-negative diagnoses. Indeed, negative SPT responses are typically used to confirm the absence of immunoglobulin E (IgE)-mediated allergic reactivity in cases in which the NPV is greater than 95%. However, one could ask whether an allergist would be comfortable sending patients who have a negative SPT home, with a risk that in 5 of 100 cases they might react. Furthermore, for many foods the NPV is significantly lower than 95%. A high rate of false-negative

results with commercial extracts (particularly plant-derived ones), is likely related to the low abundance, or the lack of stability of several allergens to endogenous enzymatic processes taking place in plant food extracts. Ho et al¹ used widely available commercial SPT extracts in a study of 906 tree nut and peanut challenges. They found that although the rate of false-negative results using the traditional 3-mm wheal cutoff for a negative SPT was 0% for walnut, it was high for almond (7%), cashew (13%), brazil nut (17%), and even peanut (8–10%).¹ The NPV for pecan was as low as 50%, similar to tossing a coin. In a recent publication from the HealthNuts study, the authors concluded that the 3-mm cutoff for a commercial cashew SPT performed as expected with high sensitivity.² However, although sensitivity may be a good outcome for a study, NPV, which depends also on the disease prevalence, is of greater clinical impact. In that study, in the context of a low specificity (48%), nearly 15% of those with a negative SPT in their population cohort were actually allergic, and 2 patients with a negative SPT required epinephrine during OFC. Akkerdaas et al³ showed that allergens, implicated in severe hazelnut-induced anaphylaxis, were sometimes not detected in SPT extracts by immunoblotting, potentially leading to a false-negative diagnosis in subjects at risk of severe reactions.³ In the case of sesame as well, commercial SPTs using a 3-mm cutoff were shown to perform below desired levels (sensitivity 84%; NPV 40%).⁴ Three of the 9 patients with false-negative SPTs had required epinephrine during OFC.⁴ In these cases, skin testing with native foods by the prick-to-prick technique showed a clearly superior performance. For example, in our previously reported NUT CRACKER study, using an SPT preparation prepared from fresh tree nuts or tree nut flour at fixed concentrations (10 mg/mL), the rate of false negatives was extremely low (4.5% for pecan, 3.8% for hazelnut, and 0% for walnut, cashew and pistachio).⁵ In the case of sesame, a high protein extract (100 mg/mL) made of sesame flour demonstrated NPV of 100%.⁴ Rancé et al⁶ found that the NPV of fresh foods was higher compared with the respective commercial SPT extracts for diagnosing egg, peanut, and

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cow's milk allergy, leading the authors to conclude that fresh foods should be used for primary testing of these allergens.⁶ The superiority of fresh foods over commercial extracts was demonstrated for many additional foods, including fish, shellfish, and wheat.^{7–9} Therefore, for many foods what should be the most important characteristic of commercial extracts, namely, their ability to exclude food allergy, is more reliably achieved with the use of fresh foods for SPT.

Another important criterion for providing reproducible results requires that commercial reagents be standardized, namely, that their composition is known and their potency is determined on a lot-by-lot basis. Unfortunately, the reagents available for foods are not standardized, resulting in significant variability among allergen extracts. For some foods such as milk, egg, peanut, and some tree nuts, 95% PPVs using commercial extracts have been established. However, the lack of standardization may impact on the reliability of these cutoffs. One study, comparing SPT extracts for 18 foods from 3 different companies, concluded that the differences observed were of low clinical relevance.¹⁰ However, very few (<10) allergic patients were diagnosed for most foods, limiting the ability to draw firm conclusions. Moreover, high variability was seen, with NPVs ranging from 85% to 94% for egg, and PPVs ranging from 53% to 72% for peanut.¹⁰ Another study found clinically significant variability between hazelnut reagents from 9 different companies, and even between 2 different batches from the same company.³ Similar variability was found for commercial extracts of fish and shellfish.^{7,8} Given these differences in allergen concentrations between different companies and between different batches from the same company, cutoffs described for SPT extracts may not necessarily apply for other extracts from the same or from other companies, thereby questioning their utility. Moreover, cutoffs for 95% PPV were not identified for many other foods. Naturally, prick-to-prick testing using fresh foods would be impossible to standardize, and they would not be able to provide cutoffs for 95% PPV better than commercial extracts. However, SPT extracts prepared from fresh foods or flour, made at fixed concentrations, were

reported to provide cutoffs for 95% PPV even to foods where commercial SPTs failed.^{4,5}

In summary, the main advantage to using fresh foods for SPT, beside their superiority in diagnosing OAS, is their potency and better sensitivity and NPV, enabling them to decrease the chances of missing a truly allergic patient at risk of severe reaction. Therefore, in cases where the results of commercial preparations are negative and the history is unclear, the use of fresh foods for SPT can minimize patient risks as well as the need to do unnecessary oral food challenges. Skin prick test preparations made at fixed concentrations from fresh foods or flour might pave the way for SPT extracts with better potency and standardization.

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