

## Short communication

# Reactivity to potential cross-reactive foods in fruit-allergic patients: implications for prescribing food avoidance

**Background:** Prescribing therapeutic elimination diets in patients with fruit allergy should include recommendations on which other foods of the same family or group may be safely consumed. Evidence-based data on the management of fruit allergy are lacking; therefore, advice may vary from just avoiding the offending fruit, to overly restrictive diets of the entire botanical family. The aims of this investigation were to assess clinical reactivity to potential cross-reactive foods in fruit-allergic patients, and the implications for prescribing specific therapeutic elimination diets.

**Methods:** Sixty-five adults diagnosed with clinical allergy to one or more fruits were evaluated for IgE-mediated allergy to other related foods, which might share cross-reactive antigens. Those with actual allergy to some *Rosaceae* fruit (including peach, apple, apricot, plum, and almond) underwent skin prick testing (SPT), food-specific IgE assessment by the Pharmacia CAP-FEIA system, and oral challenges with the entire group. For those with allergy to other fruits (chestnut, melon, banana, kiwi, or avocado) immunologic and clinical reactivity to all five were evaluated. Since a number of people in the study also had proven clinically allergy to some nut or legume (peanut, sunflower seed, walnut, pistachio, or hazelnut), the reactivity to the entire set was investigated.

**Results:** Thirty-four of those tested (52%) were found to be clinically allergic to more than one fruit, so 125 allergic reactions occurred in the 65 patients. Peach, melon, kiwi, apple, and banana accounted for 72% of allergic reactions. Forty-two (65%) had sensitization to pollens, causing seasonal allergic rhinitis and/or asthma, and 18 (28%) were sensitized to latex. The 65 with IgE-mediated fruit allergy underwent 351 additional SPT and food-specific IgE determinations with potential cross-reactive foods considered in this study; 223 (64%) of these results were positive. The routine challenges with potential cross-reactive foods uncovered 18 further reactions in 14 (22%) out of 65 (to avocado in seven; apricot in three; plum in one; almond and peanut in one; banana and hazelnut in one; avocado, banana and kiwi in one). Only 8% (18/223) of positive results for SPT, or food-specific IgE levels of greater than 0.35 kU<sub>A</sub>/l to potential cross-reactive foods investigated in this study, were clinically relevant.

**Conclusion:** Elimination diets that rely on total group avoidance, or only on the results of allergy testing, might have resulted in unnecessary restriction of 205 foods in the 65 people studied. The lack of routine oral challenges with related fruits—before prescribing dietary restriction—may have allowed 18 food reactions in one-fifth (14/65) of patients to be overlooked.

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Key words: cross-reactivity; double-blind placebo-controlled food challenge; fruit allergy (hypersensitivity); IgE antibodies; therapeutic elimination diet.

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When there is not a history of severe anaphylaxis, diagnosis of food allergy is based on a careful clinical history followed by allergy testing and oral challenges (1). Once the diagnosis of clinical allergy is established, the only proven therapy is strict elimination of the offending food (2). However, prescribing an appropriate elimination diet should include recommendations on which other

potentially cross-reactive foods, such as other members of the same botanical family, could be safely consumed. Bernhisel-Broadbent (3) performed a meaningful literature-based review to make allergists acquainted with clinical implications of cross-allergenicity among foods. Based on controlled studies evaluating clinical cross-reactivity among members of plant and animal species (4–9), it was stated that, as a rule, it is clinically and nutritionally unwarranted to restrict entire food families, particularly legumes, cereal grains, egg and chicken, and

**Abbreviations:** DBPCFC: double-blind placebo-controlled food challenge; KU<sub>A</sub>/l: kiloUnits of allergen-specific IgE per litre.

milk-cooked beef. These recommendations outlined that fish-allergic patients should be tested specifically by oral food challenge in a controlled setting before being advised that any fish species to which they show a positive skin test could be safely consumed. Advice for more extensive restriction, including avoidance of the entire food family, was suggested for people with proven IgE-mediated allergy to one member of the tree nut or shellfish families. Subsequently—and although controversy still exists—most authors advise complete avoidance of tree nuts by peanut-allergic patients (9, 10). Regarding fruits, our previous studies have shown about 50% clinical cross-reactivity among foods of the *Rosaceae* family (11). Evidence-based data on the management of fruit allergy are lacking, however, so advice varies from just avoiding the offending fruit, to overly restrictive diets of the entire botanical family. The purpose of this study was, therefore, to evaluate reactivity to potential cross-reactive foods and examine the implications for prescribing therapeutic elimination diets in people allergic to fruits.

## Material and methods

### Study Population

The study included 65 consecutive adults diagnosed with IgE-mediated clinical allergy to fruits over 1 year, in the Food Allergy Unit of the Hospital Universitario Doce de Octubre (Madrid, Spain). The diagnosis was made from history and confirmed by positive results of allergy testing by skin tests (SPT), and/or food-specific IgE antibodies, and oral challenge. Patients underwent initial open food challenges; the positive ones were followed by double-blind placebo-controlled food challenges (DBPCFC). A final in-hospital open-feeding followed all negative blinded challenges. Food challenge was not carried out in patients with a convincing history of recent severe anaphylaxis to the food (defined as marked laryngeal edema, significant wheezing, or hypotension) which developed immediately after isolated ingestion of the suspected food and required emergency management.

### Assessment of allergy to potential cross-reactive foods

After initial clinical diagnosis of IgE-mediated fruit allergy, reactions to potential cross-reactive foods were evaluated by SPT, food-specific IgE determinations, and oral provocations. Potentially cross-reactive foods were considered to be peach, apple, apricot, plum, and almond, in subjects with allergy to one member of the *Rosaceae* family, and chestnut, melon, banana, kiwi and avocado in those allergic to some of these foods, commonly associated with latex allergy. Since a number of patients included in the study also had proven clinical allergy to some nut or seed (including peanut, sunflower seed, walnut, pistachio, or hazelnut), immunologic and clinical reactivity to the entire set was investigated. Patients found to be clinically allergic to almond were evaluated for reactivity to *Rosaceae* fruits and nuts; those allergic to chestnut were assessed for reactivity to melon, banana, kiwi, avocado, and nuts. The study was approved by the ethical committee of our hospital and informed consent was obtained from each subject. The revised nomenclature for allergy from the EAACI nomenclature task force has been used throughout this manuscript (12).

### Allergy testing

Skin prick tests were performed with fresh peach, plum, apricot, strawberry, apple, melon, banana, kiwi, and avocado (provided by the patient) by the prick-prick technique as described elsewhere (13). SPT with white bean, pea, lentil, chickpea, broad bean, soybean, peanut, chestnut, walnut, sunflower seed, pistachio, hazelnut, and almond extracts (LETI Laboratories, Madrid, Spain) were carried out using a standard technique with a Prick-Lancette (ALK-Abello, Madrid, Spain). Negative and positive controls for skin testing were saline solution and histamine dihydrochloride (10 mg/ml), respectively. A positive SPT result was defined as a wheal of 3 mm or greater in diameter (after subtracting the diameter of the wheal induced by the diluent control). On the same day, venous samples were drawn, the serum was separated and stored at  $-20^{\circ}\text{C}$  until analysis. Serum samples from all patients were analyzed for food allergen-specific IgE antibodies using the Pharmacia CAP-FEIA System (Pharmacia & Upjohn Diagnostics, Uppsala, Sweden). The cutoff value for a positive result was set at 0.35 kU<sub>A</sub>/l of antigen-specific IgE antibodies.

### Oral food challenges

Actual clinical reactivity was first evaluated by open food challenges (OFC). Subjects showing a positive reaction on open provocation were subsequently challenged in a double-blind fashion as described elsewhere (14, 15). The fresh food was masked in a vehicle containing a mix of orange and pineapple juices, sugar, wheat meal, and liquid coloring (McCormick, Hunt Valley, USA). Randomization and preparation of each challenge was performed in the Allergy Laboratory of the Hospital Universitario Doce de Octubre (Madrid, Spain). Subjects were challenged first randomly with either food or placebo (vehicle), divided in five doses given every 15 min. The verum and placebo challenges were performed on two separate days. After each challenge the patient was observed for 3 h. Confirmation by DBPCFC was accepted if the subject had symptoms after provocation with the active substance, and no symptoms after the placebo challenge. Open-feeding of the food in usual quantities followed all negative blinded challenges.

## Results

Table 1 depicts individual foods proven to induce 125 allergic reactions in 65 adults diagnosed with IgE-mediated clinical fruit allergy. The median age at the time of diagnosis was 25 years, with a range of 14–70 years, and a female:male sex ratio of 1.7. Forty-two out of the 65 (65%) had sensitization to pollen causing seasonal allergic rhinitis and/or asthma; 18 (28%) had latex sensitization. Thirty-one patients (48%) were found to be clinically allergic to only one fruit, 20 to two fruits, 8 to three fruits, 3 to four fruits, 1 to five fruits, 1 to six fruits, and 1 to seven fruits.

### Reactivity to potential cross-reactive foods

The 65 patients with IgE-mediated fruit allergy had 351 additional SPT and food-specific IgE determinations, performed with potentially cross-reactive foods considered in the study; of these 223 (64%) results were positive. SPT or food-specific IgE determinations were positive to apricot in 31/35 (89%) subjects, to walnut in 11/14 (79%),

Table 1. Foods implicated in allergic reactions of 65 adults with confirmed clinical fruit allergy. The 65 patients studied had proven clinical allergy to some fruit, and 12 of the 65 were also allergic to some nut or legume. Diagnosis was made from history, and confirmed by SPT, food-specific IgE assessments, and oral challenges (unless there was recent convincing history of severe anaphylaxis)

|                | Patients* |    | Positive DBPCFC† | "Convincing" anaphylactic history |
|----------------|-----------|----|------------------|-----------------------------------|
|                | n         | %  |                  |                                   |
| Peach          | 38        | 58 | 31               | 7                                 |
| Melon          | 21        | 32 | 19               | 2                                 |
| Kiwi           | 11        | 17 | 7                | 4                                 |
| Apple          | 10        | 15 | 6                | 4                                 |
| Banana         | 10        | 15 | 7                | 3                                 |
| Chestnut       | 6         | 9  | 2                | 4                                 |
| Apricot        | 5         | 8  | 2                | 3                                 |
| Walnut         | 5         | 8  | 5                |                                   |
| Plum           | 4         | 6  | 4                |                                   |
| Hazelnut       | 4         | 6  | 3                | 1                                 |
| Almond         | 3         | 5  | 2                | 1                                 |
| Peanut         | 3         | 5  | 3                |                                   |
| Avocado        | 2         | 3  | 1                | 1                                 |
| Sunflower seed | 2         | 3  | 2                |                                   |
| Pistachio      | 1         | 2  | 1                |                                   |

\* Thirty-four patients (52%) were allergic to more than one fruit, therefore there were 125 food allergies in the 65 patients.

† DBPCFC: double-blind placebo-controlled food challenge.

Table 2. Results of allergy testing (skin prick tests and food-specific IgE assessments) and oral challenges with potential cross-reactive foods in 65 patients diagnosed with clinical fruit-allergy. Potential cross-reactive foods (not mentioned as offenders in the histories) were considered: peach, apple, apricot, plum, and almond in those allergic to one member of *Rosaceae* family; chestnut, melon, banana, kiwi, and avocado in those allergic to some of these foods; and peanut, sunflower seed, walnut, pistachio, hazelnut, chestnut, and almond in those with proven clinical allergy to some nut

|                | Total n | Positive results n (%) |           |    |
|----------------|---------|------------------------|-----------|----|
|                |         | SPT/CAP-RAST†          | Challenge | %‡ |
| Avocado        | 31      | 22 (71)                | 8 (26)    | 36 |
| Banana         | 23      | 14 (61)                | 2 (9)     | 14 |
| Kiwi           | 22      | 17 (77)                | 1 (5)     | 6  |
| Chestnut       | 37      | 22 (59)                | 0         | 0  |
| Melon          | 12      | 3 (25)                 | 0         | 0  |
| Peach          | 2       | 2 (100)                | 0         | 0  |
| Apple          | 30      | 23 (77)                | 0         | 0  |
| Apricot        | 35      | 31 (89)                | 3 (9)     | 10 |
| Plum           | 36      | 27 (75)                | 1 (3)     | 4  |
| Almond         | 43      | 26 (60)                | 1 (2)     | 4  |
| Peanut         | 16      | 8 (50)                 | 1 (6)     | 13 |
| Sunflower seed | 17      | 7 (41)                 | 0         | 0  |
| Walnut         | 14      | 11 (79)                | 0         | 0  |
| Pistachio      | 18      | 4 (22)                 | 0         | 0  |
| Hazelnut       | 15      | 6 (40)                 | 1 (7)     | 17 |
| Total          | 351     | 223 (64)               | 18 (5)    | 8  |

† Positive results of skin prick tests (SPT) or food-specific IgE levels of greater than 0.35 kU<sub>A</sub>/l.

‡ Positive oral challenges/positive SPT or food-specific IgE levels of greater than 0.35 kU<sub>A</sub>/l (%).

to kiwi in 17/22 (77%), to apple in 23/30 (77%), to plum in 27/36 (75%), to avocado in 22/31 (71%), and to banana in 14/23 (61%) (Table 2). The lowest rates of immunologic reactivity (positive SPT, or food-specific IgE levels of greater than 0.35 kU<sub>A</sub>/l) were found to melon (3/12 patients; 25%), and to pistachio (4/18; 22%).

Actual clinical reactivity to other foods (considered in this study to share cross-reactive allergens with those inducing allergic reactions) was explored by 358 open challenges and 25 sets of DBPCFC. These routine challenges uncovered 18 further reactions in 14 (22%) out of the 65 patients (Table 2). Seven patients reacted to avocado (three had allergy to melon; one to chestnut/banana; one to peach, kiwi, and melon; one to peach, apple, plum, and melon; and one to peach, apple, almond, sunflower seed, hazelnut, banana, and melon); three reacted to apricot (one had allergy to peach; one to peach, apple, and peanut; and one to peach, plum, walnut, banana, and melon); one patient found to be allergic to peach and melon reacted to plum; one patient with allergy to peach and walnut reacted to almond and peanut; one patient with allergy to peanut and chestnut reacted to banana and hazelnut; and one allergic to chestnut and melon reacted to avocado, banana, and kiwi. Only 8% (18/223) of positive results of SPT or food-specific IgE levels of greater than 0.35 kU<sub>A</sub>/l to potential cross-reactive foods investigated in this study were clinically relevant.

## Discussion

Following initial diagnosis of actual IgE-mediated fruit allergy, we explored reactivity to other foods that were not suspected of causing allergy through the clinical history, but which might share cross-reactive allergens. These investigations yielded 223 additional positive results of allergy testing, but only 18 of these were proven to induce reactions through oral challenges. This finding undoubtedly supports current recommendations against exclusion of the complete botanical family in patients who are allergic to one member of a family (3). From another perspective, a total of 205 foods might be unnecessarily restricted if the results of allergy testing were used as a basis for prescribing therapeutic elimination diets.

It has been recognized that immunologic cross-reactivity of allergens is a common problem of diagnostic procedures, especially in food allergy (16). Since the late 1980s, a number of cross-reactive fruit allergens have been identified, such as class I chitinases (17), thaumatin-like proteins (18), Bet v 1 homologs (19), lipid transfer proteins (20, 21), and profilins (22); all of which could be responsible for the extensive immunologic reactivity found in patients included in the present study. Nonetheless, the existence of cosensitization rather than cross-reactivity could not be excluded, since *in vitro* inhibition experiments were not performed in our study. Likewise, only a minor part of these (cross-reactive or not) IgE

antibodies were involved in the induction of clinical food allergy. Therefore, SPT and food-specific IgE assessment for other members of the botanical family or related foods, without oral provocations, may significantly increase the number of misdiagnoses and provide an erroneous guide for therapeutic elimination diets.

The current investigation revealed further reactions to 18 foods which had not been reported by the patients as problem foods. These reactions may be the result of chance or clinical cross-reactivity among fruit species. The symptomatic responses to avocado, banana, and kiwi were uncovered in patients with symptomatic allergy to chestnut and melon, melon, chestnut, kiwi and melon, chestnut and banana, and melon and banana. These findings suggest that class I chitinases from avocado, chestnut, and banana could be some of the potential cross-reactive food allergens.

Regarding melon, the lack of identification of its allergens still prevents explanation of potential cross-reactivity with other fruits implicated in the latex-fruits syndrome (23). In this way, our current *in vitro* studies

dealing with elucidating its antigenic structure and its relationship with other fruits and latex. The uncovered reactions to *Rosaceae* fruits were found in patients with clinical allergy to peach and plum, peach and apricot, and only peach. In this group, food allergens with homology to PR-10 (Bet v 1 homologs) and PR-14 (lipid transfer proteins) type proteins could be responsible for potential cross-reactivity. Elimination diets that are restrained to fruits reported by history as offenders, and proven to induce allergic symptoms, might overlook the risk of potential clinical cross-reactivity when the patient has not taken related foods after the reaction. Therefore, the diagnosis and management of IgE-mediated fruit allergy should consider that other foods of the same plant family (*Rosaceae* fruits) or antigenically linked ones (i.e., avocado, chestnut, kiwi, banana) should be specifically tested by oral challenge before being advised that they can be safely consumed. SPT and *in vitro* tests should be acceptable only as frontline diagnostic tools, not to be used to identify allergies to potential cross-reactive foods but as a screen for selecting foods to be evaluated through oral challenge.

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