Randomized, double-blind, crossover challenge study in 53 subjects reporting adverse reactions to melon *(Cucumis melo)*

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Background: Few studies have evaluated IgE-mediated hypersensitivity to melon with details of clinical reactions confirmed by double-blind, placebo-controlled, food challenges (DBPCFCs).
Objective: We sought to investigate clinical features (type and severity of reactions, age at onset, results of skin prick and in vitro tests, and incidence of other allergic diseases and associated food allergies) of acute allergic reactions to melon confirmed by DBPCFCs.
Methods: Fifty-three consecutive adult patients complaining of adverse reactions to melon were included in the study. Skin prick tests and detection of specific IgE were performed in all patients with melon, avocado, kiwi, banana, chestnut, latex, pollen, and other offending foods. Patients first underwent an open food challenge, unless they had a convincing history of severe anaphylaxis. Positive open food challenge reactions were subsequently evaluated by DBPCFCs.
Results: Actual clinical reactivity was confirmed in 19 (36%) of 53 patients. The most frequent symptom was oral allergy syndrome (n = 14), but two patients experienced life-threatening reactions, including respiratory symptoms and hypotension. The positive predictive value for a skin prick test was 42%, and that for specific IgE measurement was 44%. Forty-five reactions to 15 other foods were confirmed in 18 patients. The most common foods associated with melon allergy were avocado (n = 7), banana (n = 7), kiwi (n = 6), watermelon (n = 6), and peach (n = 5). Onset of melon-induced allergic symptoms occurred from 6 to 45 years (median, 20 years), preceded by seasonal rhinitis, asthma, or both in 88% (15/17).
Conclusion: About one third of reported reactions to melon are confirmed by means of DBPCFC, which has been proven to be the most reliable procedure in the diagnosis of clinical fruit allergy. Isolated melon allergy is rare, with most patients either having allergic rhinitis, asthma, or both and associated food allergies. (J Allergy Clin Immunol 2000;106:968-72.)

Key words: *Melon; food hypersensitivity; double-blind, placebo-controlled, food challenge; Cucurbitaceae; skin prick test; clinical study; fruit*

Abbreviations used
DBPCFC: Double-blind, placebo-controlled, food challenge
OAS: Oral allergy syndrome
SPT: Skin prick test

Melon *(Cucumis melo)* belongs to the gourd family, Cucurbitaceae, which also includes cucumbers, pumpkins, squashes, and watermelons. It is not clear whether it originated in Africa or Asia, but it was described by the Roman naturalist Pliny the Elder as "a new form of cucumber" in the first century AD. At present, melons are cultivated worldwide in warmer regions and greenhouses and appear in many shapes and sizes. Honeydew, cantaloupe, and muskmelon represent some of the most common hybrids and cultivars.

The initial report of melon sensitivity was closely linked to the early description of the oral allergy syndrome (OAS). In 1970 Anderson et al[1] reported a case series of patients with ragweed allergy who experienced oral symptoms after eating various melons (eg, watermelon, cantaloupe, and honeydew) and bananas. Ortolani et al[2] described a frequent association between allergy to grass pollen and some vegetable hypersensitivity, such as tomato, melon, and watermelon. In a study of patients with pollen allergy, about one fifth of the patients demonstrated dual specific IgE sensitivity to melon and pollen.[3] Specific IgE determination and immunoblot experiments suggest that common antigenic epitopes exist between melon and Plantago pollen and melon and grass pollen.[4,5]

Additionally, there are anecdotal reports of anaphylactic reactions to melon and ethanol-induced anaphylaxis after the ingestion of overripe melon.[6,7] In the last several years, melon sensitivity has been associated with latex sensitivity. Several studies have highlighted clinical and immunochemical cross-reactivity between latex and one or more of the following: banana, chestnut, avocado, and kiwi. This is described as the latex-fruit syndrome.[8-12] More recently, Brehler et al[13] detected specific IgE antibodies to a wide variety of fruits, including melon, in 69% of serum samples of 136 patients with latex allergy. Cross-reacting IgE antibodies to latex, melon, and other fruit allergens were demonstrated by using RAST-inhibition tests. Therefore although some studies have evaluated the frequency of immunologic reactivity to melon and potential cross-reac-

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tive pollen and latex allergens, there is little information about melon allergy. The purpose of this study is to provide a detailed clinical evaluation of reactions to melon confirmed by double-blind, placebo-controlled, food challenges (DBPCFCs) in 53 consecutive patients reporting adverse reactions to this food.

METHODS

Subjects

Over an 18-month period, 53 consecutive adult patients referred to the Food Allergy Unit of the Hospital Universitario Doce de Octubre (Madrid, Spain) complaining of adverse reactions to melon were enrolled in the study (male/female ratio, 0.47). The median age was 24 years, and the age range was 15 to 69 years. Twenty-eight of 53 subjects experienced several adverse reactions before the consultation (8 patients with 2-5 reactions to melon and 20 patients with >5 reactions).

Diagnostic procedures

The first diagnostic stage consisted of a medical and dietary history, including questions on family history, other diseases, offending foods, number of episodes, symptoms, time between intake and onset of the symptoms, minimum amount of food to produce symptoms, other causes of the patient's complaints, physical exertion and its relationship to the symptoms, treatment in the emergency department, and medications used. Skin prick tests (SPTs) were performed on each patient with fresh melon, avocado, banana, and kiwi (provided by the patient) by using the prick-prick technique[14]; chestnut and latex extracts; and inhalant allergens (ALK-Abello Laboratories, Copenhagen, Denmark). SPTs were also done with other offending foods mentioned in the history. 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). Negative and positive controls for skin testing were saline solution and histamine dihydrochloride (10 mg/mL), respectively. On the same day, blood samples were drawn and stored at –20°C. Serum samples were tested for IgE-specific antibodies to melon, avocado, banana, kiwi, chestnut, latex, and other offending foods mentioned in the history by means of fluorometry (ImmunoCAP, Pharmacia, Uppsala, Sweden), as detailed by the manufacturer.[15] The cutoff value for a positive result was set at 0.35 kU_A/L of antigen-specific IgE antibodies.

Actual clinical reactivity to melon, avocado, banana, kiwi, chestnut, and other offending foods mentioned in the history was first evaluated by means of open food challenges. Subjects showing a positive reaction on open provocation were subsequently challenged in a double-blind, placebo-controlled fashion, as described elsewhere.[16,17] The suspected food was masked in a vehicle containing a mix of orange and pineapple juices, sugar, wheat meal, and liquid coloring (McCormick, Hunt Valley, Md). Cumulative food doses for the food challenges were 200 g of fresh melon, 20 g of ground nuts, and 17 g of freeze-dried food for the remaining substances. Randomization and preparation of the challenges were performed in the allergy laboratory. Subjects were challenged first randomly with either food or placebo (vehicle). The interval before the second part of the DBPCFC was at least 24 hours. Confirmation by DBPCFC was accepted if the subject had symptoms after provocation with the active substance and no symptoms after the placebo challenge. An open feeding of the food in usual quantities followed all negative blinded challenges. Food challenge was not performed when a patient had a convincing history of recent severe anaphylaxis to the food, which was defined as objective findings (marked laryngeal edema, significant wheezing, or hypotension) that developed immediately after the isolated ingestion of the suspected food and required emergency management within the last year.

TABLE I. Challenge results in 53 patients reporting adverse reactions to melon

	Patients	
	No.	%
Reported reactions to melon (n = 53)		
Convincing anaphylactic history	2/53	4
Positive initial OFC responses	25/51	49
Positive DBPCFC responses	17/25	68
Positive final OFC responses	0/8	0
Overall clinical reactivity	19/53	36

OFC, Open food challenge.

RESULTS

Clinical features

Eighty-four oral challenges with melon (59 open food challenges and 25 DBPCFCs) were performed under observation in 51 of 53 patients reporting adverse reactions to this food. In the 51 patients with an initial open challenge, 25 reactions were positive. However, DBPCFCs confirmed only 17 (68%) of 25 reactions (Table I). Clinical manifestations in these patients appeared within 30 minutes after intake and included isolated OAS (14 patients); facial angioedema and OAS (1 patient); facial angioedema, rhinoconjunctivitis, and OAS (1 patient); and OAS and wheezing (1 patient). In addition, two reactions considered positive were based on a recent "convincing" history of melon-induced anaphylaxis. These patients experienced life-threatening reactions, including oropharyngeal symptoms, generalized urticaria and angioedema, nausea, vomiting, wheezing, and hypotension, less than an hour after isolated melon ingestion. Overall, actual clinical reactivity was confirmed in 19 (36%) patients reporting adverse reactions to melon. Fifteen (79%) of the 19 patients had positive SPT results for melon, specific IgE for melon, or both. Table II lists the sensitivity and specificity of SPTs and specific IgE with melon when compared with DBPCFCs or convincing histories of recent anaphylactic reactions.

Other allergies

Table III summarizes other allergies found in the 19 patients with clinical reactivity to melon. These patients reported 76 reactions to 29 other foods. Eighteen patients had positive SPT reactions, specific IgE, or both with 23 other foods, and 13 patients had positive test responses for latex. All patients clinically reactive to melon were challenged with 4 foods (kiwi, avocado, banana, and chestnut) and other foods reported as offenders in the clinical history, unless this was contraindicated by a convincing history of recent anaphylaxis. Overall, 18 of 19 patients with melon allergy had a total of 45 reactions to 15 other foods (38 by DBPCFCs and 7 on the basis of a convincing history of an anaphylactic reaction). The most common foods causing reactions in melon-sensitive

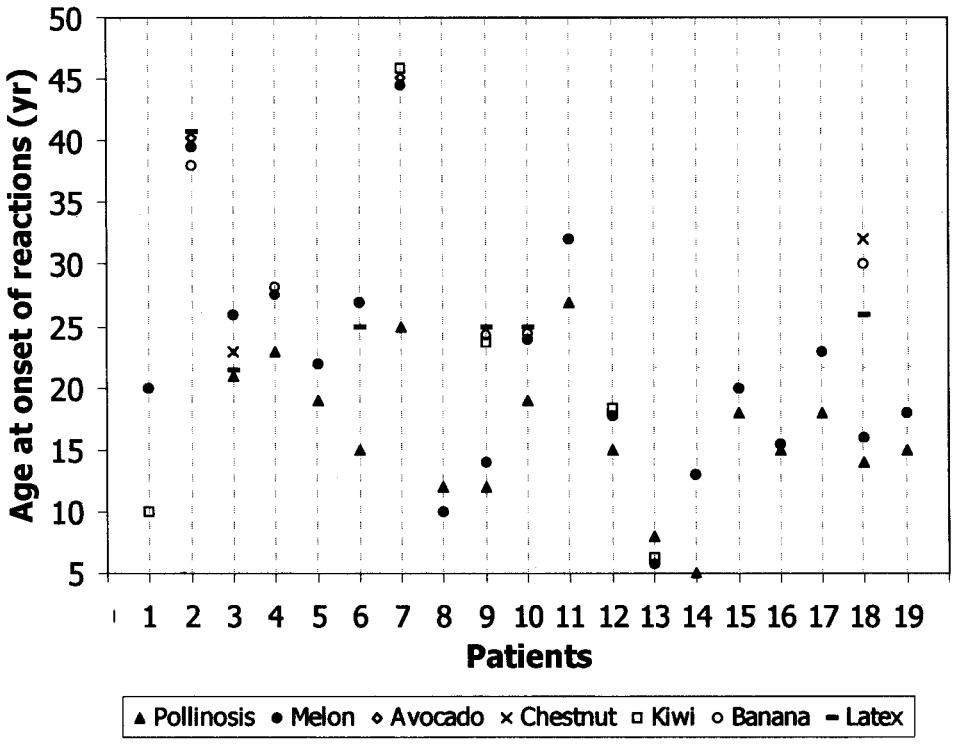

FIG 1. Age at onset of seasonal rhinitis, asthma, or both and symptoms with melon, avocado, kiwi, banana, chestnut, and latex in 19 patients with actual clinical allergy to melon.

TABLE II. Performance characteristics of the SPTs and the specific IgE measurements for melon and the outcome of DBPCFCs or convincing histories of anaphylactic reactions to melon in 53 patients

	SPTs	Specific IgE measurement
No. of patients with positive results	68% (54%-80%)*	43% (30%-58%)
Sensitivity	79% (54%-93%)	53% (30%-75%)
Specificity	38% (23%-56%)	62% (44%-77%)
Positive predictive value	42% (26%-59%)	44% (24%-65%)
Negative predictive value	77% (50%-92%)	70% (50%-85%)

*Values in parentheses are 95% confidence intervals.

patients were avocado (7 patients), banana (7 patients), kiwi (6 patients), watermelon (6 patients), and peach (5 patients). In patients who had given a history of reacting to the food challenges, test results confirmed the sensitivity in 2 of 2 with avocado, 6 of 8 with banana, and 5 of 8 with kiwi. The remaining sensitivities to these 3 fruits were uncovered in the course of routine challenges with these fruits, which were conducted in all 19 melon-sensitive subjects.

Eighteen (95%) of 19 patients had seasonal rhinitis, asthma, or both with positive SPT responses to multiple grass, tree, and weed pollens.

Age at onset

The age at onset of seasonal rhinitis, asthma, or both and reactions induced by melon, avocado, kiwi, chestnut, banana, and latex is shown in Fig 1. The age at first reaction to melon ranged from 6 to 45 years (median, 20 years). Seasonal rhinitis, asthma, or both preceded the first reaction to melon in 15 (88%) of 17 patients with these data available.

DISCUSSION

Since first reported by Anderson et al[1] in 1970, very few studies have evaluated IgE-mediated hypersensitivity to melon, giving a detailed clinical analysis of reactions confirmed by DBPCFC. In our case series, we found definite clinical reactivity in 19 (36%) of 53 patients reporting adverse reactions to melon. Initially, among the 51 patients who underwent open food challenges with melon, 25 were considered positive. However, DBPCFCs reproduced only 17 (68%) of 25 reactions. As in other studies,[18-20] skin testing and in vitro tests provided limited guidance for the clinical diagnosis; the positive predictive value was 42% for SPTs and 44% for specific IgE measurements. Using basic scientific principles, several investigators consistently proved the value

TABLE III. Other allergies in 19 patients with actual clinical reactivity to melon

		Foods															Latex		
		SPT					Specific IgE					Oral challenges							
Patient No.	Age (y)	A	C	K	B	Other	A	C	K	B	Other	A	C	K	B	Other	SPT	Specific IgE	Seasonal rhinitis, asthma, or both
1	20	+	+	+	–	P, E, T	+	+	+	+	P, E, T, S	–	–	+	–	E	–	+	+
2	40	+	+	+	+		+	+	–	+		*	–	–	*		+	+	
3	26	+	+	+	+		+	+	–	+		+†	*	+†	+†		+	+	+
4	28	+	–	+	+	P, Ap, L, F, Pl, W, Wb, Chp	–	–	–	–		–	–	–	+	P, Ap, F,* Pl, W	–	–	+
5	23	+	+	+	+	Wm	+	–	+	+	Wm, Ch	–	–	–	–	Wm, Ch	–	+	+
6	27	+	+	+	+	P	+	+	+	+	P	+†	–	–	–		+	+	+
7	48	+	+	+	+	F	+	+	+	+	T	+	–	+	–		–	+	+
8	18	+	+	+	–	P, Ap, Pl	–	–	–	–	P	–	–	–	–	P, Pl	–	–	+
9	24	+	+	+	+	P, Ap, W, T, Pl, Cu, Wm, Bb, Pch	+	+	+	+	P, Ap, T, Pl, Cu	–	–	+	+	P, Ap, T,* Wm	–	+	+
10	25	–	–	+	+	P, Wm, T	–	–	–	–		–	–	–	+	Wm, T	–	–	+
11	33	+	+	+	+	P	+	–	–	–		–	–	–	–	P	–	+	+
12	18	+	+	+	–	P, Ap	+	+	–	+	P, Ap	+†	–	+	–		–	+	+
13	15	–	+	+	–		–	–	–	–		–	–	+	–		–	–	+
14	17	–	–	+	+	P, Wm, Pi	–	–	+	+	P, Pi	+†	–	–	–	P,* Wm	+	+	+
15	20	+	+	+	+	P, Wm, Or	+	+	–	+	Or	–	–	–	–	Wm, Or	–	+	+
16	30	–	–	–	–		–	–	–	–		–	–	–	–		–	–	+
17	26	+	+	+	+	Wm	+	+	+	+		+†	–	–	–	Wm	+	+	+
18	36	+	+	+	+	Bi	–	–	–	–		–	+	–	*	Bi	+	+	+
19	21	+	–	–	–		–	–	–	–		–	–	–	+		–	–	+

A, Avocado; *C,* chestnut; *K,* kiwi; *B,* banana; *other,* other positive results; *P,* peach; *E,* eggplant; *T,* tomato; *S,* strawberry; *Ap,* apricot; *L,* lentils; *F,* fig; *Pl,* plum; *W,* walnut, *Wb,* white bean; *Chp,* chick peas; *Wm,* watermelon; *Ch,* cherry; *Cu,* cucumber; *Bb,* broad bean; *Pch,* pistachio; *Pi,* pineapple; *Or,* orange; *Bi,* bilberry.

*Not challenged because of a convincing history of severe anaphylaxis.

†Not ingested before oral challenges.

of a double-blind, placebo-controlled challenge to study these apparent food-related signs and symptoms. This technique has been established as state of the art for the evaluation of adverse reactions to foods.[16,21,22] However, it has seldom been used in the evaluation of adverse reactions to fruits, particularly in the context of the OAS. The lack of contact between the food and the oral mucosa when given in capsules and the lability of allergens from fruits and other vegetables have been invoked against its usefulness in evaluating adverse reactions to fruits, which are frequently manifested as local oropharyngeal signs and symptoms. However, practical difficulties could be overcome by using fresh fruits in liquid vehicles, as recommended by Noe et al.[17] In our practice we use freeze-dried fruits and other vegetables in liquid vehicles for double-blind challenges, which are always followed, when the reaction is negative, by an open feeding under observation. We had no false-negative results, with the exception of two early patients given freeze-dried melon; after that we used fresh melon. In our case series, no patients with negative DBPCFC responses with fresh melon in liquid vehicle had an adverse reaction in the final open provocation.

As described previously,[1] the most common clinical feature associated with melon allergy was OAS in the context of pollinosis. However, 2 (11%) of the 19 patients had severe reactions that began quickly, within a few minutes after ingestion of melon, with pruritus inside the mouth. This progressed rapidly with feelings of respiratory difficulty, generalized urticaria, and hypotension. Thus melon allergy should be considered not only a cause of local oropharyngeal signs and symptoms in patients with allergy to pollen but also a potential cause of life-threatening reactions.

In addition, our patients reported multiple reactions with other foods of vegetable origin, as in other studies evaluating patients with fruit allergy.[23,24] SPT responses, specific IgE levels, or both were positive for 23 of 29 different foods reported as offenders, including kiwi, avocado, banana, chestnut, peach, tomato, fig, and pineapple, all of which have been reported to share IgE-binding components with latex. However, only 45 of 76 reported reactions to 15 foods other than melon were confirmed by objective procedures. We decided to test reactivity to 4 foods (avocado, banana, kiwi, and chestnut) and latex in each patient clinically allergic to melon to analyze the relationship between immunologic and clinical reactivity. In this way, it is worth pointing out two practical relevant findings. First, although only two patients reported an adverse reaction after ingesting avocado, challenges elicit-

ed reactions in another 5 patients who had never eaten this food or at least had not eaten it recently. Thus potential reactions to foods, such as avocado, kiwi, and chestnut, should be considered in these patients when there is no clear evidence of recent ingestion with complete tolerance. Second, there was an important difference between results of SPTs and in vitro tests and provocation with these foods. Therefore only oral challenges should be useful for establishing a comprehensive elimination diet in patients with the latex-fruit syndrome.

Finally, most patients with melon allergy had several episodes before seeking specialist consultation, probably because the oral symptoms were not thought to be significant for the adult patient himself or herself, the family practice physician, or both. This fact provides some retrospective insights into the natural history of melon allergy and the latex-fruit syndrome. Almost all patients (18/19) with clinical melon allergy had positive results on SPTs to tree, grass, and weed pollen and seasonal rhinitis, asthma, or both. Eighty-eight percent (15/17) reported an earlier onset of seasonal respiratory symptoms than melon symptoms. The gap between the time of onset of clinical reactions to melon, avocado, kiwi, and chestnut was less than 1 year in 6 of 11 patients who remembered the age of onset of their first symptoms. Interestingly, in 3 patients symptoms to these foods started within a period of 10 or more years. We do not know whether initially they had specific IgE antibodies to all these foods and clinical symptoms started progressively over several years or, alternatively, whether IgE responses were developing followed closely by clinical reactions. Because there is a reported extensive cross-reactivity among these foods, these patients probably had simultaneous immunologic responses to these foods and later had scattered clinical responses. At present, it is well known that cross-reactivity can elicit positive in vitro or SPT results in subjects who do not display any clinical symptoms, thus giving rise to the so-called asymptomatic sensitization. Therefore considering the broad range of immunologic responses to foods of vegetable origin lacking associated clinical symptoms, only proper diagnosis of food allergy on the basis of objective procedures to evaluate clinical reactivity may avoid confusion and unnecessary elimination diets.

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