TÜBİTAK

Turkish Journal of Medical Sciences

http://journals.tubitak.gov.tr/medical/

Research Article

Turk J Med Sci
(2018) 48: 469-475
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doi:10.3906/sag-1705-140

An evaluation of banana allergy in children living in the Mediterranean region

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Received: 26.05.2017 • **Accepted/Published Online:** 05.10.2017 • **Final Version:** 14.06.2018

Background/aim: We aimed to apply a double-blind placebo-controlled food challenge (DBPCFC) test to patients who reported a reaction to banana and showed positivity for banana-specific IgE in Turkey.

Materials and methods: Medical data of patients who had been analyzed for banana allergy were reviewed, focusing on banana-specific IgE positivity at the Department of Pediatric Allergy-Immunology at the Akdeniz University Faculty of Medicine between the years 2004 and 2012. Patients were called to the clinic for a DBPCFC test.

Results: A total of 47 patients participated. We determined reactions in 13% of DBPCFC patients. A cut-off value was determined as 0.66 kU/L for banana-specific IgE, and sensitivity and specificity were 83% and 51%, respectively. The positive predictive value for specific IgE was 20% while the negative predictive value was 96%. Sensitivity and specificity for banana prick-to-prick test (P + P) was 33% and 93%, respectively; positive predictive value was 40% and negative predictive value was 91%.

Conclusion: This is the first study conducted in Turkey to use a DBPCFC test in the diagnosis of banana allergy. Up until now, the positive predictive value was not defined for banana-specific IgE. Our study showed that specific IgE or skin tests alone are not adequate for the diagnosis of food allergy; to define subjective symptoms related to food and to determine cross-reactions, DBPCFC tests should be done for confirmation.

Key words: Allergy, banana, challenge test, children, profilin

1. Introduction

Food allergy is defined as an abnormal or exaggerated immune response against proteins in food. Although little is known about banana allergy, it is known that the allergenic properties of banana are highly complex. Allergens such as Mus a 1 (a profilin) and Mus a 2 (class 1 chitinase), which can cause cross-reactions, are present in banana. This has clinical significance as there can be cross-reactions with foods such as kiwi and avocado, as well as pollen and latex. However, there are also cases of banana allergy with no cross-reaction.

Plant food allergies are often difficult to diagnose. Furthermore, the evaluation of methods used in T cell-mediated allergy, as well as in IgE-mediated allergy, might not always be simple. The sensitivity of commercial skin testing products is usually less than 40% (1). The prick-to-prick (P + P) test applied with fresh fruit is known to be more useful for diagnosis, although P + P test data with respect to negative and positive predictive values of all foods are insufficient. When evaluating the clinical history along with P + P tests, the sensitivity of fruit-specific IgE has been reported to be approximately 37% (1). However, the most accurate method for diagnosis of all food allergies is the double-blind placebo-controlled food challenge (DBPCFC) (2). This is important for verification of both IgE and non-IgE reactions.

Although there has been a reported increase in the number of symptomatic patients, there are few studies regarding the clinical features and the diagnostic approach for children with banana allergy (3–6). In this study, we aimed to determine banana allergy in children who had positive banana-specific IgE.

2. Materials and methods

2.1. Study group

Data were examined from the files of patients who had banana-specific IgE positivity (>0.35 kU/L) and presented at the Department of Pediatric Allergy-Immunology at the Akdeniz University Faculty of Medicine between the years 2004 and 2012. Specific IgE positivity was detected in a total of 248 cases. All patients were contacted by telephone and asked to describe their reaction to banana and other foods. Patients who indicated that they had a reaction were called to the clinic for a DBPCFC test. None of the patients

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reported anaphylaxis. A total of 47 patients underwent testing in the clinic. Informed consent was obtained from all patients or their parents. Patients who no longer had any symptoms with banana, patients who had moved to another city, and patients whose parents did not sign the informed consent were excluded from the study. Approval for the study was granted by the institutional review board. The data of the participating patients were recorded on patient history forms (2) created for this study. These data consisted of family history, comorbid diseases, suspected foods, resulting symptoms, the time elapsed between food intake and reaction, number of reactions experienced, number of emergency service visits, medications used, means of food intake, physical examination findings, and requirement for medical treatment after the encounter. Tests were applied according to the following scheme (Figure).

2.2. Serum total IgE and specific IgE

The data from the patient files were examined. Total IgE and specific IgE (ImmunoCAP, Pharmacia, Uppsala, Sweden) values were recorded.

2.3. Allergy skin test (epidermal prick test, EPT)

All patients who reported symptoms with banana consumption (n = 47) underwent allergy skin testing with a standard commercial solution. Both the standard commercial solution test and the P + P test were performed for the evaluation of food sensitivity (egg white, egg yolk, cocoa, cow's milk, wheat flour, tomatoes, peanuts, strawberries, bananas, nuts, beef, chicken, fish, sole fish, hazelnuts, orange, soybeans, pears, kiwi, and avocado). A skin test with a standard solution was performed for respiratory (grass, weed-grain, weeds, trees, *Olea*, *Pinus*, and *Acacia*) and latex allergens. Allergopharma (Reinberk, Germany) standard solutions were used for the food, respiratory, and latex allergen skin tests. Histamine dihydrochloride (10 mg/mL) was used as a positive control while physiological saline was used as a negative control. Histamine was evaluated at 10 min and the allergens were assessed after 15 min. For commercial solution tests and P + P, the widest diameter of the induration (wheal) and its perpendicular diameter were measured. When the positive control edema was >3 mm with no reaction in the negative control, the case was considered positive in the EPT.

2.4. Food challenge test

After a 15-day period of food elimination, all patients (n = 47) underwent DBPCFC for banana. Every day during the test, food and placebo were freshly prepared individually for each child (Table 1). To avoid confusion and any associated risks during interventional studies, the tests were started at 0900 hours after a minimum of 4 h of fasting. The patients were under observation for 8 h until the test finished at 1700 hours. In the study, the same technician prepared the foods and the placebo. A doctor tested the similarity of taste and smell. The patients, as well as the doctor who observed the patients, were blinded to the contents for accuracy of evaluation. The subjects were challenged in a double-blind placebo-controlled fashion as previously described (7,8).

Active and placebo nutrients were given on the same day according to their protocols. Dose intervals were set to 15 min. After the administration of the active and/or placebo mixture, the patients were observed for 2 h. The mixtures were given in increasing doses until a cumulative dose of 100 g was reached. If the patient started with the placebo, the active food was administered after a 2-h observation period. Patients who started with the active food mixture received the placebo after a 2-h period of observation. The patient and observing physician were blinded to the sequence of administration of foods and placebo.

The results of the test were evaluated by a different person according to the protocol previously described (2) for the oral food challenge test (OFCT) scoring scheme. The tests of the patients who had an allergic reaction were

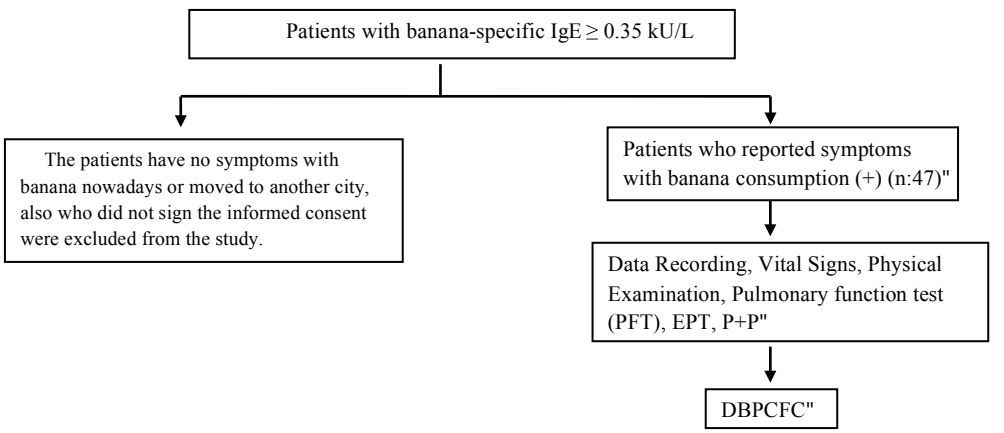

Figure. Following scheme.

Table 1. Active and placebo food preparation (8).

Active food		Placebo	
Banana	100 g	Pear	100 g
Sugar	13 g (1 tbsp.)	Sugar	13 g (1 tbsp.)
Wheat meal	11 g (1 tbsp.)	Wheat meal	11 g (1 tbsp.)
Peppermint syrup	12 mL (1 tbsp.)	Peppermint syrup	12 mL (1 tbsp.)
Coffee	50 mL	Coffee	50 mL
Saffron	Amount on point of knife	Saffron	Amount on point of knife

terminated, the amount of food that caused the reaction was recorded, and recommendations were made. The open food was given to patients who did not have a reaction.

2.5. Statistical analyses

The MedCalc (version 11.2.1.0, Belgium) program was used for statistical analyses. As the DBPCFC test was taken as the gold standard, the ROC analysis was performed to evaluate the diagnostic performance of the skin test, IgE, and P + P tests. Based on the results of the analysis, sensitivity, specificity, likelihood ratio (LR) of positivity and negativity, and positive and negative predictive values (PV) were calculated.

3. Results

The families of a total of 248 patients with specific IgE positivity were contacted by telephone, 47 of whom reported symptoms and had been admitted to the hospital. None of the patients had described anaphylaxis as a symptom.

The patients comprised 31 (66%) males and 16 (34%) females, with a mean age of 6.2 ± 2.1 years. Atopy was present in 41 cases (87%), and 33 (70%) had a family history of atopy. The most common complaint was wheezing in 28 (60%) patients, with other complaints of atopic dermatitis (AD) in 11 (23%), allergic rhinitis (AR) in 7 (15%), asthma in 6 (13%), urticaria in 4 (9%), and gastrointestinal symptoms (GIS) in 3 (6%). Wheezing and AD comorbidity was reported by 5 (11%), asthma and AR comorbidity by 4 (9%), wheezing and AR comorbidity by 2 (4%), AR and AD comorbidity by 1 (2%), and GIS, asthma, and AR comorbidity by 1 (2%).

In 42 of 47 cases, total IgE and the absolute number of eosinophils were evaluated. The median of total IgE was determined as 271 (min–max: 34.4–5000) kU/L, while the mean absolute eosinophil count was determined as 415 ± 309/mm^3 (min–max: 60–1500). The average banana-specific IgE level of all cases was 0.81 ± 0.53 kU/L. Of all the patients who underwent the DBPCFC test, banana P + P positivity was detected in 5 (11%) patients, although all patients were negative for banana EPT, which was applied with standard allergens. In 19 (40%) patients, at least one positive EPT test (with fresh foods or standard allergen solution) against banana or banana cross-reactivity was observed. A reaction was observed in 6 (13%) patients who were administered the DBPCFC test. The 6 patients with DBPCFC test positivity had no positive test for EPT. Two of them had positive P + P tests with 5 mm and 4 mm. The mean banana-specific IgE value was 0.611 ± 0.25 for patients with DBPCFC test positivity. Although 16 (34%) of the patients had banana-associated symptoms, their DBPCFC test results were negative, but their results for cross-reactivity were positive. Although these patients had no EPT positivity, the P + P test was positive for 3 of them (respectively 4 mm, 3 mm, 4 mm). The mean banana-specific IgE value was 0.80 ± 0.49 in these patients. The details of the patients are shown in Tables 2–4. Pollen sensitization was detected in 3 of the DBPCFC-positive cases and 12 of the DBPCFC-negative cases with banana-associated symptoms and positive cross-reactive allergen test (Tables 2 and 4).

The sensitivity for banana P + P was determined as 33%, while the specificity was found to be 93%. The positive predictive value was 40% and the negative predictive value was 91% when the cut-off value for specific IgE was taken as 0.66 and cut-off wheal size was taken as 3 mm (Table 5).

4. Discussion

There are insufficient data in the literature reporting on the clinical findings and diagnostic methods for evaluating banana allergy in children (4–6,9-11).

In the current study, the epidermal prick test and P + P test with fresh fruit were applied to children with a reported banana allergy who were positive for banana-specific IgE. After the DBPCFC test, the children were diagnosed with banana allergy and both the clinical and laboratory parameters of these children were evaluated. Only 13% of children who reported banana allergies and tested positive for banana-specific IgE were found to be truly allergic to banana. In 34% of these cases, sensitivity to banana cross-reactivity was detected. Zeinab et al. (11)

Table 2. Laboratory results of DBPCFC-positive cases.

	AEC (mm^3)	IgE (kU/L)	EPT	EPT	EPT	EPT	P + P	P + P	P + P	P + P	Specific IgE (kU/L)	DBPCFC
			Pollen	Banana	Other	Latex	Banana	Kiwi	Avocado	Pear	Banana	
11	400	316	-	-	-	-	-	-	-	-	0.42	+
16	100	214	p	-	-	-	-	-	-	-	0.62	+
18	200		g	-	-	-	+	+	+	+	0.66	+
22		137	-	-	-	-	-	-	-	-	1.07	+
23	60	790	w, tm	-	c	-	+	+	+	+	0.55	+
39	500	254	-	-	-	-	-	-	-	-	0.35	+

tm: Tree mixture; g: grass; p: *Pinus*; w: weed; c: cocoa.

Table 3. Properties of DBPCFC-positive cases.

	Age (years)	Sex	Complaint	Atopy	DBPCFC	Reaction time (min)	Reaction type	Therapy requirement
11	4	M	AD exacerbation	+	+	420	AD	+
16	6	M	Urticaria	+	+	30	Urticaria	+
18	5	M	Wheezing, AD	+	+	5	Urticaria	+
22	6	F	Wheezing	+	+	30	Wheezing	+
23	10	F	Wheezing	+	+	30	Angioedema	+
39	6	M	GIS symptoms, asthma + AR	+	+	360	GIS symptoms	+

AD: Atopic dermatitis; AR: allergic rhinitis.

analyzed the atopic patients with or without reactions to banana and performed EPT, P + P, and banana-specific IgE tests. They used OFCTs to demonstrate the ones who were suspected of having the allergy. OFCTs were positive in 7.5% of patients having positive history. None of the atopic patients with negative history had a reaction in OFCTs.

Banana is an important source of nutrients; the fruit is both grown and consumed in high amounts, especially in the Mediterranean region. However, no studies have been conducted to investigate the diagnostic approach and clinical presentation of banana allergy in children living in the Mediterranean region. IgE-mediated banana allergy often causes class 2 food allergies (6). Food allergens are rapidly absorbed in the oral cavity and destroyed by the digestive system enzymes. Class 1 nutritional allergens that are thought to sensitize via the gastrointestinal tract maintain their allergenicity even after digestion. Class 2 allergens are heat-labile and susceptible to the digestive process. Class 2 allergens are partially homologous to proteins in certain fruits and vegetables. The clinical findings for banana allergy usually present as mild local symptoms (oral allergy syndrome), but severe symptoms progressing to anaphylaxis have also been reported (5). In the current study, anaphylaxis was not observed in any of the patients who tested positive for the challenge test. However, symptoms such as urticaria, angioedema, wheezing, exacerbation of atopic dermatitis, and gastrointestinal symptoms were observed. It could be speculated that geographical factors might account for the difference in reaction.

The reaction can be observed in patients with banana cross-reactive allergies. However, these reactions are complicated and highly variable. IgE-mediated latex–fruit syndrome is becoming an important health issue. Significant cross-reactivity between food and inhalant allergens was demonstrated in several studies (1,9,10,12,13). The term latex–fruit syndrome has been used to describe the cross-reactivity between latex and fresh fruit allergens. The plant foods involved in latex–fruit syndrome are banana, avocado, chestnut, kiwi, and

Table 4. DBPCFC negative but banana-associated symptoms and cross-reactive allergen test positive cases.

	Age (years)	Sex	Complaint	AEC (mm^3)	IgE (kU/L)	EPT	EPT	EPT	EPT	P + P	P + P	P + P	P + P	Specific IgE (kU/L)	DBPCFC
						Pollen	Banana	Other	Latex	Banana	Kiwi	Avocado	Pear	Banana	
1	9	F	Asthma	200	233	-	-	-	-	-	+	-	-	1	-
5	3	M	Wheezing	470	88	p	-	s	-	-	-	-	-	0.47	-
9	10	F	Asthma + AR	1000	1660	g, gg, w, tm	-	f	-	+	-	-	-	0.38	-
12	5	M	Wheezing	600	34.4	-	-	-	-	-	+	-	-	1.51	-
13	12	F	Asthma + AR	1500	1443	g, gg, w	-	-	-	-	-	-	-	0.37	-
19	6	M	Wheezing, AD	300		g, gg, w, o	-	-	-	-	-	-	-	1.32	-
25	7	F	AD	400	580	gg	-	-	-	-	+	-	-	0.40	-
26	7	F	Wheezing	300	240	g, gg	-	-	-	-	-	-	-	0.42	-
29	7	M	GIS symptoms	450	2000	-	-	-	-	-	-	+	-	0.968	-
30	5	F	AD, wheezing	980		g, gg, w, tm, o, p, a	-	ew, cm, wf, pn	+	+	+	+	+	1.24	-
31	7	M	Wheezing	192	113	-	-	-	-	-	+	-	-	0.37	-
32	10	F	Asthma + AR	150		g, gg, w, o	-	-	-	-	+	+	+	0.56	-
37	7	M	AD, wheezing		79.4	g, gg	-	-	-	-	-	-	-	0.38	-
40	7	F	Wheezing	276	286	g, gg	-	-	-	-	-	-	-	1.17	-
43	6	M	AR		779	g, gg, w, tm	-	-	-	+	+	+	+	1.88	-
47	10	M	Asthma	110	439	p	-	-	-	-	-	-	-	0.44	-

a: *Acacia*; tm: tree mixture; g: grass; gg: grass-grain; p: *Pinus*; w: weeds; o: olives; f: fish; wf: wheat flour; s: strawberry; pn: peanuts; cm: cow's milk; ew: egg white.

Table 5. Sensitivity, specificity, and predictive values of specific IgE and P + P test.

		% Sensitivity	95% CI	% Specificity	95% CI	+ LR	+ %PV	–%PV
Banana P + P	+	33	4.3–77.7	93	80.1–98.5	4.56	40	91

*When the cut-off value for specific IgE was taken as 0.66 and cut-off wheal size was taken as 3 mm.

mango. Class 1 chitinase (Hev b 11) has been identified in chestnut, banana, and avocado. The N-terminal region of Hev b 11 is an important latex allergen related to cross-reactivity (1,9,10,12–15). The primary diagnostic tool for latex allergy is medical history, prick test, and serum-specific IgE levels. The P + P test that is used with fresh fruits is generally a better predictor of clinical reactivity when compared to commercial extracts and sensitivity is 80% and 40%, respectively (1).

Grob et al. (4) evaluated children and adults with a history of allergic reaction to banana and specific IgE response but without any latex response. Four patients with a history of reaction after banana consumption underwent skin tests with respiratory allergens, latex, banana, avocados, and kiwi. In those cases, sensitivity to at least one banana cross-reactivity was determined.

Due to immunological susceptibility, banana has a high level of cross-reactivity. Studies have demonstrated that putative panallergens such as Mus and profilin, which are present in banana, are responsible for pollen–food cross-reactions. In half of the current study patients, banana allergy was confirmed with the DBPCFC test and banana cross-reactivity was revealed. In the remaining children, other cross-reactive allergies, such as to pollen, can be expected to occur in the years to come. The natural history of this type of banana cross-reactive allergy is unclear. In our study pollen sensitization was detected in 3 of the DBPCFC-positive cases.

Fruits and vegetables undergo denaturation during the creation of commercial skin test solutions and lose their allergenicity. Therefore, the P + P technique is used to test fresh fruits and vegetables. In our study, the P +

P test was positive in two patients whose banana allergy was diagnosed based on DBPCFC. There are no reported studies investigating the positive and negative predictive value of the P + P test in the diagnosis of banana allergy. In addition, to the best of our knowledge, there are no studies on T-cell allergies that lead to P + P positivity.

In the current study, no positivity was detected in EPT performed with commercial preparations in patients who presented with banana-specific IgE positivity and suspected history. In the literature, there is a report of an EPT-negative case with banana allergy-associated anaphylaxis (5). Studies have reported that Mus a5-induced skin test positivity is rare, but it has high IgE-binding capacity (3). Banana positivity in the P + P test might be present because the test was applied with a banana sample that contained all the banana proteins. These findings show once again that evaluation of banana allergy with the EPT test applied with commercial preparations is not optimal. Therefore, the P + P test can be recommended for use as more valuable in the evaluation of banana allergy.

In the current study, 2 out of 6 patients who were positive for the DBPCFC test also had P + P positivity in kiwi and avocado tests. In 3 cases, there was pollen EPT positivity. Sensitivity for at least one banana cross-reaction was detected in all the current patients who reported banana-related symptoms and had specific IgE positivity but negative results for the DBPCFC (Table 4). This variation in the results might be related to differences in the Mus proteins to which the patients were sensitive. This study was conducted during the pollen off-season and during a time of low banana consumption. Therefore, pollen-sensitive patients might not have reacted to banana because of the low pollen count, but might have shown a pollen season-related suspicious reaction history. In addition, the patients with GIS and AD exacerbation might have shown a non-IgE-mediated allergic reaction to banana and may have therefore been negative for the IgE-mediated tests.

Banana contains five allergy-causing allergens (Mus a1, Mus a2, Mus a3, Mus a4, and Mus a5). Mus a1 might cause a cross-reaction with profilin, pollen, and plants. Allergenic profilins, which are involved in pollen–food syndrome, have been identified in trees, grass, weed pollen, vegetables, fruits, and latex. In pollen-sensitive individuals profilin sensitivity can be detected even in situations where allergic sensitivity cannot be detected. It generally results in a mild reaction, like an oral allergy syndrome. Profilin plays an important role in the formation of allergies to some fruits such as banana, melon, watermelon, tomatoes, citrus fruits, and persimmon (16). In the current study, the absence of positivity to pollen and food tests in half of the patients (3/6) who reported a history of allergic reaction to banana and whose diagnosis was verified by the DBPCFC test might be explained by profilin sensitivity. In addition, all 3 of these patients might be atopic and might develop positivity towards allergens later in life. However, profilin sensitivity was not evaluated in this study.

The double-blind food challenge test is the gold standard for diagnosis of subjective symptoms. In this study, none of the patients who had negative DBPCFC results developed a reaction after the food was given openly. These results demonstrated the accuracy of the method.

Genetics plays an important role in predisposition to allergic diseases. In the current study 33 (70%) cases involved a family history of allergic diseases.

There are some limitations to this study. The most prominent is that our patients were not observed for more than 8 h for diagnosis of non-IgE-mediated reactions. Second, the sensitivity to profilin and other allergenic molecules that might be important in banana allergy could not be evaluated. Third, the number of cases with a verified allergic reaction to banana was small.

The assessment of sensitivity to allergenic molecules present in banana that are involved in cross-reactions might prove difficult and DBPCFC is the most valuable test for these kinds of evaluations. Children who are allergic to banana might also be sensitive to other foods. However, further studies are needed for a detailed analysis of allergenic proteins in banana.

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